TO MY BROTHER

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THE OGBUEFI NNANYELUGO OF ONITSHA.

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BREAST CANCER IN NIGERIA

THESIS

submitted for the Degree of

DOCTOR OF MEDICINE

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by

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INTRODUCTION

Malignant growths have taken their toil in human mortality and morbidity so that for centuries now, men have occupied their life-time collecting data on various tumour types, classifying and typing them, studying their natural biological behaviour, their aetiological factors, and the means of treating or preventing them, thus striving to eradicate these scourges. Europe and America had always been in the forefront of research and study of cancer, but the African continent has not been completely neglected and this study therefore, is centred in Nigeria with a population of about 70,000,000 (seventy million) and situated on the West Coast of Africa. This is a fast developing country facing the problems of any other developing country such as steady increase in population, housing, education, health care and social welfare of the people. The health problems are more complex and difficult in Nigeria where there are inadequate numbers of hospitals, medical personnel and inadequate vital statistics to meet the need of the nation. The Nigerian govenmment, in tackling the nation's health problems, has already established teaching hospitals in Lagos, Ibadan, Ife, Zaria, Nsuka (Enugu) and Benin (see fig. 1) and recently has planned to build more teaching hospitals in various other states of the Federation. Health authorities

in planning the welfare of the community need to have knowledge of the incidence, diagnosis and possible aetiological factors and available treatment for various diseases. Early in the history of medical practice in Nigeria, doctors have been mainly concerned with assessing the incidence of individual infective diseases such as Tuberculosis, Leprosy, Amoebiasis, Malaria, Schistosomiasis, which are still taking their toll in overall mortality and morbidity in the population. These diseases however,. can now be readily investigated, diagnosed and treated. The question of malignant diseases in Nigeria has not received similar authentic documentations as has been done in other developed parts of the world. Breast cancer in Nigerian females and males has therefore been chosen for a retrospective study in order to provide data on neoplasis from tropical Africa with the hope that striking differences such as exposure to environmental factors or genetic factors will permit international comparison which may lead to the hypothesis as to the aetiology of breast cancer in the world.

PART ONE

THE HISTORICAL BACKGROUND TO THE STUDY

CHAPTER I

HISTORICAL REVIEW IN THE LITERATURE

Renner (1910) was the first to observe the rarity or absence of cancerous and other malignant growths in the aborigines of Sierra Leone, but noted the increase in Creoles, (i.e. African slaves returned from West Indies and America after abolition of slave trade). He was of the opinion that the Creoles had adopted European habits, and were more likely to acquire European diseases including malignant growths. His belief was strengthened, when he observed the rarity or absence of tumours in the indigenes, the Fantis of the Gold Coast, who he believed to have resisted the inroads of European civilisation.

Hoffman (1915) referred to Renner's observation and said that when every reasonable allowance was made for the want of accuracy and completeness in the available returns for the African continent, it would seem safe to assume that cancer was of a relatively very low degree of frequency in African countries, even among the white population of European origin, and that tumours were extremely rare.

Macfie (1923) reported on the prevalent diseases of the Gold Coast (now Ghana) and stated that tumours were probably as common as elsewhere, but sarcomas appeared to be rather more frequent

than carcinomas.

Sharp (1923) confirmed Macfie's observation that carcinomas were rare but differed in this respect from sarcomas among the population of the coastal towns of West Africa. In observing the extreme rarity of carcinoma in Northern Nigeria he was induced to send his only case of mammary carcinoma in an old woman from Sokoto, Northern Nigeria, to the Museum of the Royal College of Surgeons. He believed that it would have been easy to observe cases of breast carcinoma among the 9,000,000 (nine million) inhabitants of Northern Nigeria where "women do not commonly cover their breasts".

Blair (1923) over a twenty-one year period in Nigeria claimed that he never saw a case of carcinoma or sarcoma. However, he observed that occasional carcinomas had been found by medical men in the coastal regions and that these occurred chiefly in natives who had come into contact with the Europeans.

Alder and Cummings(1923)recorded eight cases of malignant growths in Sierra Leone. These included: 1 melanotic sarcoma of the foot; 2 "epitheliomas" (squamous carcinomas), one from the scrotum and the other from the lip; 1 breast carcinoma; 3 liver tumours, 2 being primary cancers and the other secondary; and 1

meningio-sarcoma with metastases. They were of the opinion that Europeanisation, whether or not it were conducive to the spread of malignant growth, would certainly be responsible for intelligent natives affected by them consulting medical officers. Thus civilisation may have been wrongly blamed for the spread of the disease, when it has only been responsible for its diagnosis.

The search for cancer in African natives also extended to Eastern parts of Africa. The Kenya Medical Journal (1924) reported a case of carcinoma of stomach presenting as gastric outlet obstruction in a Kikuyu woman. It also stated that a case of squamous carcinoma arose in a scar of an old burn, and a case of carcinoma of the cervix uteri had also been reported in African patients. Apprently carcinomas were not unknown in that part of the continent, but it was still generally suggested that cancer was a rare disease among African natives.

Miller (1924) reported the first case of breast carcinoma in an East African woman. Jewell (1924) treated five cases of malignant tumours in East African natives. These included: 3 cases of "orbital sarcoma"; 1 case of sarcoma of the parietal and frontal bones and 1 case of squamous carcinoma of the dorsum of the foot (who died with secondaries in all internal organs). He also treated

several patients with breast carcinoma, cancer of the cervix, squamous carcinoma of the lip, rodent ulcer, and cancer of the vocal cords in Seychelles Creoles. He concluded that malignant diesease was certainly less common among the black races than among the white, but that it was not nearly so rare as a perusal of the earlier literature would lead one to suppose.

Mason (1927) reported six cases of malignant growth in Mombasa. These included two cases of breast carcinoma, and the remaining four were squamous carcinoma of the foot, and of the abdominal wall, carcinoma of the nose, and squamous cell carcinoma of the lower end of the oesophagus.

Chand (1927) described primary malignant lymphoma of the stomach with post mortem findings of "lymphoblastoma" in kidney, lymph nodes and stomach in an African tribesman.

Smith and Elmes (1934) and Vint (1935) collected relatively large series of malignant growth in Nigeria, and Kenya Africans (500 and 546 cases respectively). Their compiled relative ratio frequencies are presented in Table 1.

TABLE I

Relative Ratio Frequencies of Cancers in Nigeria & Kenya

Tumour Types	Nigeria (500)	Kenya (546)
Carcinoma	48.6%	50.7%
Sarcoma	36.0%	34.4%
Melanoma	8.0%	10.8%
"Endothelioma"	3.4%	2.7%
Teratoblastoma	0.4%	2.5%
Chorio-carcinoma	0.2%	2.3%
Renal cell carcinoma	-	0.1%

Des Ligneris (1936) reviewed 2,973 cases of malignant tumours in the Union of South Africa. Of these 2,909 (74.3 per cent) were in the people of European origin, 431 (14.5 per cent) in African natives and 233 (7.8 per cent) in so called "Coloured". He found also that cancer occurred fairly frequently in the South African Bantus, but not nearly as frequently as in Europeans. There were observed differences between Europeans and natives as regards the various types and localization of cancer. These differences seemed to indicate that the occurrences of each type and localization was

bound up with certain kinds of irritation and that the frequency of cancer was directly related to the frequency of this type of irritation.

On African male breast carcinoma, Davies (1949) in East Africa collected 69 cases of mammary cancer and observed that 5 of the cases were in males. Elsewhere in Africa, he revealed that a similar high relative incidence of mammary cancer in males had been noticed. He expressed, as percentage of all mammary cancers the incidence of male breast cancer in Nigeria, Cameroon, Kenya and Uganda as shown in Table II below:

TABLE II

The Percentage Incidence of Male Breast Carcinoma in four African Countries (Davies 1949)

Country	Percentage
Nigeria	10% and 8% (Two separate readings
Cameroon	27%
Kenya	20%
Uganda	7.8%

Edington (1956) collected only 2 male breast carcinomas out of 64 mammary cancers in the population of Gold Coast he studied, and concluded that breast cancer in males would appear to be relatively more common in the Gold Coast than in Europe, the aetiological agent in its production perhaps being gynaecomastia, a not uncommon finding in malnutrition and cirrhosis of the liver.

Thus earlier workers on cancer in African natives, Smith and Elmes (1934), Vint (1935), des Ligneris (1936), Davies (1949) and Edington (1956) had established that cancer of all types occur in various organs in both Europeans and Africans alike and that sarcomas and male breast carcinomas are more prevalent in Africans.

By 1960, with support of the British Empire Cancer Campaign, "Cancer Registry" was introduced in various British colonies, including one in the Pathology Department, University College Hospital, Ibadan. This has introduced a new method of approach to the question of cancer in the African continent, and it has enabled Edington and Maclean (1965) to carry out a cancer rate survey in Ibadan, and Pearson (1963) to study clinical aspects of breast carcinoma in 100 Nigerian females. Other European

authors in various parts of Africa at this era focused their attention mainly on cancer incidence rate in the continent, e.g. Uganda, Davies, Knowelden and Wilson (1965), Portuguese East Africa, Prates and Torres (1965), South Africa, Higgins and Oettle (1960).

Doll, Muir and Waterhouse (1970) in their book on Cancer Incidence in Five Continents have recently made available the findings of most of these surveys in tropical areas and comparable findings from temperate climates are included. Apparently, very much is now known on cancer incidence rate in Africa, but not much attention has been paid on the survey of histological epidemiology on individual organ malignant lesions, except where such lesions are almost entirely confined to the tropics e.g. Kaposi sarcoma and Burkitt's lymphoma. For this reason, the present study will concern itself with cancer of the breast, a specific organ of the body. Attempt will be made to review the literature, focus attention on epidemiology of Breast Cancer and Pathology of breast malignant neoplasis in Nigeria. The study will be based on data gathered on breast disease in the department of Pathology here for the period, 1960 to 1975, inclusive.

PART TWO

THE CURRENT STUDY

CHAPTER II

MATERIALS AND METHODS

All the available epidemiological data on all the neoplastic lesions presented here are obtained from the Cancer Registry which is located in the Pathology Department, University College Hospital, Ibadan, Nigeria. The Cancer Registry was established in 1960 with the support of the British Empire Cancer Campaign. The registry records all cases of neoplasis detected in patients living in Ibadan with its environs and in many other patients from other states in the Federation of Nigeria. All the patients are Nigerians, but because the hospital is situated in the Western State of Nigeria, the majority of them are Yorubas. A few however, are Ibos, Midwesterners and Northerners. The patients are recorded as "Ibadan cases", representing the patients from Ibadan and its environs, and "Non-Ibadan cases", representing the patients from other areas of the Federation. All the neoplastic lesions from various organs of the body, recorded in the Cancer Registry from 1960 to 1975 inclusive are diagnosed by clinicians and in most cases the diagnoses are confirmed by histology. All the lesions are classified according to the recommendation of the World Health Organisation "W.H.O." (Scarff and Torioni, 1968), and recorded.

The sex distribution and the relative ratio frequency of various tumour types are analysed. In this study, attention is mainly focused on breast diseases, particularly the neoplastic lesions. The relative ratio frequency of breast carcinoma, in relation to the total number of all the malignant lesions recorded in the Cancer Registry is first determined, and then the importance of breast carcinoma in the female and male population is surveyed. General consideration is then given to various benign and malignant female breast lesions and where possible the results are compared internationally.

In other to carry out epidemiological study on female patients that develop breast carcinoma in Nigeria, questionnaires are sent to 200 female patients with breast carcinoma and to 200 female patients without breast neoplasis, all matched for age and social status. Their names, sex, occupation, nutritional data, their drug habits, marital and fertility status are recorded for analysis. The total number of pregnancies, live births, miscarriages, and number of years spent by either cancer or control patient breast feeding a child are statistically analysed and internationally compared.

Ibadan is the capital city of the Western State of Nigeria with a well known recorded population. According to the population

census of Nigeria. Western Region (1963) Ibadan has a female population of 269,000 and a male population of 358,000. Since then no other official population census has taken place in Nigeria. In order to assess the incidence rate of breast cancer in this known figure of Ibadan population the 5-year age-group annual distribution of 246 cases of breast cancer recorded in the cancer registry over the 16 year period of this study is carried out. From this the annual incidence of breast cancer per 100,000 of Ibadan population is calculated for each age-group. The figures obtained from this, are then racially compared with those quoted for other coloured nations of the world and for the causacians by Doll, Muir, and Waterhouse in their book, Cancer Incidence in Five Continents, Vol. 2, 1970.

General pathological features of malignant lesions of breast are studied. In the Cancer Registry, 197 cases of breast malignant neoplasis are only diagnosed clinically, and as such they are not included in the histological analysis. Seventy patients, who had advanced tumours with wide spread metastases had only lymph node biopsies to confirm the clinical diagnosis of malignancy. Sections are made from biopsies taken from primary mammary lesion in 255 patients, who, for some reason, did not have operation, and

from 203 patients who had mastectomy. This means that a total of 458 patients had histological verification of their primary breast disease; of these patients, sections are available for review in 420 female patients and 17 male patients. In addition, all the sections available for benign mammary lesions are reviewed. Slides obtained from sections ranged from 2 to 8 slides per patient. All the sections are stained with Haematoxylin and Eosin, but in certain cases special stains like Gomori's silver impregnation technique, Masson trichrome, periodic acid Schiff (P.A.S.) and Oil red O, are used to demonstrate reticulin, collagen, neutral muco-polysaccharides and fat, as the case may be. The whole available sections are personally reviewed by the author. All the malignant lesions are classified according to the original histological classification of carcinoma of the breast by Foote and Stewart (1946) and adopted by McDivitt, Stewart and Berg of Armed Forces Institute of Pathology in their Fascicle on tumours of Breast (1968), and recently modified by Pathology Working Group, BreastCancer Task Force, National Cancer Institute of America (1973).

In order to establish the avenue for geographical pathology, some of the histological types of breast cancer found in Nigeria

are compared with those found in America and Japan. The relationship of benign to malignant breast neoplasis is studied, emphasis being laid on the relationship of benign fibrocystic disease to malignant breast neoplasia. For this purpose, slides of 420 patients operated upon for breast carcinoma are studied for evidence of associated fibrocystic disease. In order to determine whether there is an association between fibrocystic disease and breast carcinoma, the data obtained from 151 patients with fibrocystic disease alone, 99 patients with carcinoma and associated fibrocystic disease, and 639 patients with carcinoma only, are analysed by calculating the simple correlation coefficient. Various histological types of breast carcinoma associated with fibrocystic disease are also analysed and internationally compared where possible. Lastly, detailed study is made on some histological types of breast carcinoma seen here in Nigeria. The epidemiological study on these histological variants is internationally compared where necessary, emphasis being laid on differences in the microscopic features peculiar to African breast cancer.

CHAPTER III RESULTS:

SECTION 1: EPIDEMIOLOGY OF BREAST CANCER IN NIGERIA

(A) ANALYSIS OF ALL MALIGNANT DISEASES IN CANCER REGISTRY (1960-75)

A total of 12,455 cases of malignant lesions of various organs are recorded in the Cancer Registry from 1960 to 1975 inclusive. The patients are grouped into "Ibadan" and "Non-Ibadan" cases according to whether they come from Ibadan and its environs or from other parts of the Nigerian Federation. Table III shows the sex distribution of these cases.

TABLE III

Sex Distribution of 12,455 Cases

Ibadan Cases		Non-Ibadan Cases	TOTAL
Female	1,978	4,440	6,418
Male	1,878	4,159	6,037
TOTAL:	3,856	8,599	12,455

To find out whether there is any significant difference in the sex distribution of these malignant lesions, the null hypothesis to be tested is that about half the total number of cases should be from each sex. The 't'-test of difference between expected proportion and observed one is employed. For "Ibadan cases" only, the value of 't' is 1.25. With this value, the null hypothesis is accepted. This means that the sex difference observed could have arisen by chance, and the proportion is not statistically different from half ($\frac{1}{2}$). For "Non-Ibadan cases", the 't' value is 3.70. This means that there is very strong evidence that the observed ratio is quite different from half. In fact the finding that a higher proportion of "Non-Ibadan cases" is females is accepted. In the calculated value between the two locations, 't' $\simeq$ 1.00. That is, there is no statistically significant difference in the sex distribution. It follows that there is the same proportion of females in Ibadan and Non-Ibadan cases. When the two locations are combined, the 't' - value is 4.4. This result is statistically significant. It enables the assumption that the occurrence of malignant lesions is about the same for either sex to be rejected and it is concluded that a higher proportion of cases is from females.

Relative Ratio Frequency

There is a grand total of 3,015 cases of sarcomas including malignant tumours of the lympho-reticular system and malignant connective tissue tumours. The relative ratio frequency for all these tumours is 24 per cent. There is also a grand total of 6,890 cases of all carcinomas from various organs of the body, with a relative ratio frequency of 54 per cent. Generally, therefore, the Registry recorded more carcinomas than sarcomas in the 16-year period of the survey. The five commonest malignant neoplasms in the registry are carcinoma of the cervix, malignant lymphomas, primary liver cell carcinoma, Burkitt's lymphoma and malignant breast neoplasias. Table IV shows the total number of patients recorded for each case type along with their relative ratio frequency - (R.F.F.).

TABLE IV

Relative Ratio Frequency (R.R.F.) Of Most Common Malignant Neoplasia In The Cancer Registry (1960-1975)

Tumour Type	Number of Cases	R.R.F.
Carcinoma of cervix	1,379	11%
Malignant lymphoma	855	7%
Burkitt's lymphoma	850	7%
Primary liver cell carcinoma	842	7%
Malignant breast neoplasms	725	6%

Carcinoma of the cervix with a relative ratio frequency of 11 per cent is the commonest malignant neoplasia encountered in Nigeria. Malignant breast neoplasias are the fifth (5th) commonest malignant disease of all the malignancies in the Registry.

The most common malignant lesions found in the main female reproductive organs are carcinoma of the cervix, malignant breast neoplasia, chorio-carcinoma and malignant ovarian tumours. Table V shows the total number of cases recorded for each type during the 16-year period of the survey, along with their relative ratio frequency.

TABLE V

Relative Ratio Frequency (R.R.F.) Of Most Common Female Malignant Neoplasia

Tumour Type	Number of Cases	(R.R.F.)
Carcinoma of cervix	1,379	11%
Malignant breast neoplasias	725	6%
Chorio-carcinoma	420	3%
Malignant ovarian tumours	397	3%

Malignant breast neoplasms are second to carcinoma of the cervix as one of the commonest female malignant lesions encountered in Nigeria.

(B) GENERAL PATTERN OF BREAST DISEASES IN NIGERIA

Sections prepared from tissues obtained from breast lumps in 1, 145 female and male patients are histologically diagnosed and classified in the Registry. 1 .102 are of the female breast lesions, and 43 cases are of male breast diseases; 44 cases of these are due to infective causes, such as unresolved breast abscesses, tuberculosis and onchocerciasis. 13 cases are due principally, to fat necrosis of female breasts. 361 cases are due to benign lesions of the breast, comprising of fibrocystic disease of the breast, mammary duct ectasia, fibroadenoma, giant fibroadenoma and gynaecomastia. The remaining 725 cases are due to malignant mammary lesions, and consists of 697 cases of carcinoma, 18 cases of malignant lymphomas and 10 cases of primary sarcomas of the breast. Tables VI and VII show the precentage-sex distribution of :

(a) the recorded benign breast lesions,

and (b) the recorded breast tumours.

TABLE VI

BENIGN BREAST LESIONS

LESION	No. of Cases		TOTAL	Per-centage
	Female	Male		
Breast abscess	40	2	42	4%
Tuberculosis	1	-	1	<1%
Onchocerciasis	1	-	1	<1%
Fat necrosis	13	-	13	1%
Fibrocystic disease	124	-	124	9%
Mammary duct ectasis	27	4	31	3%
Gynaecomastia	-	8	8	1%

TABLE VII

BREAST TUMOURS

Lesion	No. of Cases		Total	Percentage
	Female	Male		
Fibroadenoma	183	-	183	16%
Giant fibroadenoma	10	2	12	1%
Carcinomas	675	22	697	61%
Malignant-lymphoma	16	2	18	2%
Sarcomas	10	-	10	2%

It is gathered from the above tables that infective agents afflict mostly the female breasts. The chronic granulomatous lesions, tuberculosis and onchocerciasis, in this series are only diagnosed in the female breasts. Fat necrosis appears solely as a female disease. Fibrocystic disease of the breast occurs mainly in the female breasts in Nigeria. Fibroadenoma has only been described in the female breast here, but giant fibroadenoma has been diagnosed in both males and females. Carcinoma is the commonest cause of breast diseases in both Nigerian female and male patients than either infective or benign breast lesions. The percentage incidence of less than one per cent recorded for gynaecomastis seems to indicate that gynaecomastia is not so common a cause of breast disease in Nigeria.

Benign and Malignant Breast Diseases

Fibroadenoma, fibrocystic disease of the breast and mammary duct ectasia are the main benign lesinns that are further discussed in this series. Fibroadenoma is the commonest of them all. Among the malignant breast lesions, carcinomas are the commonest. Primary Burkitt's lymphoma of the breast is the second commonest malignant lesion of the breast encountered here, the least common, being sarcomas of the breast. Table VIII shows the age-group distribution of the case types.

TABLE VIII

AGE-GROUP: DISTRIBUTION OF BENIGN AND MALIGNANT BREAST LESIONS

Lesion	0-10	11(12)-21	22-30	31-40	41-50	51-60	61-70	71-80	Tot
Fibroadenoma	0	71	74	17	4	0	0	0	16
Cystic disease of breast	0	20	45	36	17	4	0	0	12
Mammary duct ectasia	0	6	9	5	2	1	0	0	2
Carcinoma	0	4	78	199	198	107	144	9	63
Burkitt's lymphoma of breast	0	4	4	1	0	0	0	0	1
Sarcomas of breast	0	0	2	4	0	0	0	0	4

Both benign and malignant breast lesions do not appear to afflict the female breast from moment of birth up to 11 years of age. Starting from menarche, (12 years) up to the age of 15 years, female breasts are mostly afflicted by benign lesions, mainly fibroadenoma and fibrocystic disease of the breast. Primary Burkitt's lymphoma of the breast is the only malignant lesion that appears to afflict breasts of either female or male patients within this age group. From 16 years of age onwards, other types of malignant neoplasia may begin to afflict

the female breasts, carcinomas starting earlier than sarcomas. The commonest benign lesion during the second decade of life in the females is fibroadenoma, followed by fibrocystic disease, while the commonest malignant neoplasia during this decade, is the primary Burkitt's lymphoma of the breast.

Although carcinomas do occur at this period, their incidence rate is low. The peak age incidence of fibroadenoma is 12 to 30 years, and is the commonest tumour of the female breast below the age of 25 years. Its incidence declines with age, and it becomes rather a rare cause of female breast lesion from the fifth decade onwards. The peak age incidence for fibrocystic disease is from 21 to 40 years. It continues to be appreciably the cause of female breast disease up to the sixth decade of life and then declines with increasing age. The peak age incidence of carcinoma is 31 to 50 years. Carcinoma continues to be the commonest cause of breast lump in females from the third decade up to eighth decade of life and thereafter. Burkitt's lymphomas and sarcomas are mainly the malignant lesions of the breasts of the young. They do not appear to attack the breast after the fourth decade of life. These facts are highlighted graphically inffig. 2. The average age of patients suffering from fibroadenoma is 23 years, that of fibrocystic disease is 31 years and that of carcinoma is 43 years.

Site of Breast Lesions

Breast lesions commonly afflict either the right or the left breast, and in some cases the lesions may be bilateral. Most fibroadenomas of the breast are unilateral, only 10 patients of the recorded cases have bilateral fibroadenoma. Most of the fibrocystic disease of the breast are bilateral. Carcinomas are usually unilateral, and only 6 patients have been described to have bilateral carcinoma. Table IX shows the side of breast most commonly afflicted by diseases in Nigeria.

TABLE IX

SIDE OF BREAST LESIONS

Lesion	Right breast percentage	Left breast percentage
Fibrocystic disease	57%	44%
Fibroadenoma	52%	49%
Carcinoma	53%	45%

Lesions of the breast have a general predilection to afflict the right breast more than the left breast in Nigeria. Fibrocystic disease and carcinoma afflict the right breast more than fibroadenoma, and the latter does affect the left breast more than the rest.

Familial Incidence of Breast Neoplastic Lesions

No familial case of breast lesion, either benign or malignant, has been recorded in the Cancer Registry during the 16-year of this study. This may most likely be due to difficulty in obtaining accurate clinical history from patients who are mostly ignorant of the fact that cancer could be a cause of chronic breast ulcers that may kill.

Tribal incidence of breast Neoplastic Lesions

There is no observed tribal difference in the nature and pattern of distribution of breast lesions whether benign or malignant amongst the patients studied.

(C) GENERAL DESCRIPTIVE EPIDEMIOLOGY OF BREAST CANCER

Salient Features

Breast cancer is the fifth commonest malignant lesion of all the malignant diseases encountered in Nigeria. When all the malignant diseases affecting the main female reproductive organs are considered, breast cancer is second to carcinoma of the cervix as one of the commonest neoplastic diseases that afflict the females. It is therefore, one of the major clinical problems in Nigerian female population.

Incidence

A total of 725 malignant breast neoplasia is recorded in the Cancer Registry, for both females and males between 1960 and 1975. Ninety-seven (97) per cent of these are female cases and 3 per cent are male cases. The relative ratio frequency of breast cancer of all malignant lesions encountered in Nigeria, is 6 per cent. An average of 38 cases of breast cancer are recorded annualy in the cancer registry. Fig. 3 shows the uncorrected annual incidence figures of breast malignant lesions recorded from 1960 to 1975, inclusive. It shows an increased incidence of breast carcinoma for the years 1969-75 compared with 1960-69.

Sex, Age-Group Distribution

Table X shows the age-group and sex distribution of 658 cancer patients whose ages are known.

TABLE X

SEX, AGE-GROUP DISTRIBUTION OF BREAST MALIGNANT LESIONS

	10(16)-20	21-30	31-40	41-50	51-60	61-70	71-80	Total
Female	4	78	199	198	107	44	9	639
Male	0	0	3	5	5	3	3	19

The youngest female patient with breast carcinoma in the series is 16 years of age, and the youngest male is 31 years of age. It is observed from the table that in the female, mammary cancer begins to afflict the breast from the second decade of life onwards. Its incidence rate rises steadily thereafter until it reaches its maximum between the fourth and fifth decade, and then starts to decline gradually from the sixth decade onwards. In the male, carcinoma begins to afflict the breast at much later age than in females. It is first detected in the male breasts early in the fourth decade of life and reaches its peak between the fifth and sixth decade, and then falls slighly from the seventh decade onwards.

Average Annual Incidence by Age-group in Years

The 5-year age-group and sex distribution of breast cancer in Ibadan population estimated during the Nigerian Population Census of 1963 (since then there has never been another official census), is shown in tables XI, and table XII shows the average annual incidence per 100,000 of Ibadan population.

The mean, the median and the modal, ages of female and male patients with breast carcinoma are shown below as follows :

	Mean Age	Median Age	Modal Age
Female	43 years	43 years	40 years
Male	53 years	55 years	60 years

This figure shows that females develop breast carcinoma at a younger age than males. The peak incidence of cancer occurs in feamles at age of 40 years, and in the males at age of 60 years.

TABLE XI

ANNUAL AGE-GROUP DISTRIBUTION OF BREASTCANCER IN CANCER REGISTRY

AGE	60-61		61-62		62-63		63-64		64-65		65-66		66-67		67-68		68-69		69-70		70-71		71-72		72-73		73-74		74-75		TOTAL	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
0 - 1																																
1 - 4																																
5 - 9																																
10 - 14																																
15 - 19																																
20 - 24							1								1						1		1									4
25 - 29		2	2					1						1		1					1		1		4		2		3		18
30 - 34		2	1		1		4			1		5				3		3			3		1		4		1		2		31
35 - 39		3	2		6		2			1		4		5		1		1			2		3				3		1		34
40 - 44		1	2		4		1		3		2			4				2			2		1		5		4		1		32
45 - 49		1	2		2				1		2		2		2		2		3		2		1		1		7		1		28
50 - 54		1	5		5				1		3		1		2				3		3		5		3		2	1	2	1	36
55 - 59		1	2		1												3		1				1		3		2				14
60 - 64		1	2				1		1		3						2		3		1				2				1		17
65 - 69		2			1		1		1		1				1				5				1		1				1		15
70 - 74																	1		1		1								2		5	
75 - 79																	1															1
80 - 84															1																1	
85+																																
Age Unknown					1		1		2				2		2				1													9
TOTAL		14	18		21		11		10		13		14		1	18		14		23		16		15		23		21	1	14	2	244

TABLE XII

AVERAGE ANNUAL INCIDENCE PER 100,000 BY AGE-GROUP IN YEARS

Age Groups	Estimated Population 358,000		Total in 16 Years		Annual incidence of breast neoplasia per 100,000 Population	
	Male	Female	M.	F.	Male	Female
15-19	30,000	18,520	-	-	-	-
20-24	78,000	50,000		4		.5
25-29	61,000	43,000		18		2.8
30-34	34,000	25,000		31		8.3
35-39	21,000	14,000		34		16.2
40-44	16,000	1,100		32		19.4
45-49	9,000	6,000		28		31.1
50-54	6,000	5,000	1	37		49.3
55-59	3,000	2,000		14		46.7
60-64	3,000	3,000		17		43.6
65-69	1,300	1,000		15		100.0
70-74	1,000	1,000		5		33.3
75+	1,000	1,000	1	1		6.7
Age Unknown			1	9		
All Ages	358,000	269,000	3	244	.04	5.8

It is gathered from these tables that in Ibadan both the female and male population declines with increasing age of the people. Breast cancer begins to appear in the male population at 50-54 years age-group. Its incidence rate is constant in all the recorded age-groups. It is extrememly low, for only 3 cases are recorded during the 16-year period of this study. On the other hand, breast cancer becomes noticeable in the female population at an earlier age-group of 20-24 years. Its incidence rate rises steeply to reach its peak in females at 50-54 year age-group; from hence it declines steadily to reach the cancer incidence rate in the male population at 75 years and above.

The annual incidence of breast cancer per 100,000 of female population, rises while the population falls with rising age. It is maximum in the female at 65-69 age-group, where the population is as low as 1000, and the annual incidencer per 100,000 is 100. These points are further illustrated in figure 4. The annual incidence of breast cancer per 100,000 of Ibadan female population (269,000) for all ages is 5.8 and that of the male population (358,000) is 0.04.

(D) Specific Epidemiological Survery on 200 Breast Carcinoma Patients and 200 Control Patients without Breast Carcinoma:

The results of comparing the epidemiological features of 200 carcinoma patients with those of 200 control patients without breast carcinoma are as follows :

Marital Status

The cancer and the control patients are all married females. 70 per cent of them are married to polygamous males and 30 per cent to monogamous males.

Occupation

Some 83 (42 per cent) of the 200 carcinoma patients are farmers and petty traders, 111 (56 per cent) are housewives, and the remaining 6 (3 per cent), consist of 2 nurses, 1 teacher, 1 palm-wine seller, 1 mud-pot maker and 1 cloth weaver. All of them are however, occupationally housewives, for in Nigeria as a whole, all housewives have some form of occupation in addition to those of their husbands for sustaining their family. They all belong to low socio-economic group of Nigerian society. The chosen control patients have similar occupational pattern and the same socio-economic status as the carcinoma patients.

Diet

Their diet consists of tropical staple foods such as yam and cassava products, rice, beans and maize which form the main

sources of their carbohydrates; fish, beef, mutton, goat, and chicken which provide the bulk of their proteins, and unsaturated fats from palm and ground-nut oils which provide their main sources of fat. Their vegetables are varied and include green vegetables, bitter leaf, "Ewedu" and Okro and Agbona which are vegetables used for making stew. Pawpaw, oranges, bananas and coconuts are main sources of fruits they eat. On the whole most of the patients live on high carbohydrate and on low protein diet, and consume large quantities of unsaturated fat.

Cooking Habit

Most of the women cook their food in open fire made from dry woods of various types, and depending on their economic standard, some of them do sometimes use kerosene stoves for cooking.

Drug Habits

The majority of the cancer patients before visiting the Teaching Hospital for consultation have the habit of using some form of "traditional medicine" prescribed by the herbalists who are often their first choice of medical consultation. The traditional medicine commonly taken by most of the Yoruba patients are called "AGUNMU" and "AGBO" concoctions which

are either applied locally or taken orally for any type of diseases. These concoctions, including mouldy rice, beans and ground-nuts, have been shown to contain AFLATOXIN, a toxic principle extracted from the mould, Aspergillus Flavus (OLUMBE BASSIR, 1977). Non of the patients has any history of having taken any contraceptive "pills".

Fertility

The control patients have a total of 1,092, while the carcinoma patients have a total of 921, pregnancies among them. Table xiii shows the distribution of gravids of 200 carcinoma patients and 200 control patients.

TABLE XIII

Distribution of Gravida to 200 Carcinoma Patients and 200 Control Patients

Gravida	0	1	2	3	4	5	6	7	8	9	10	10
Carcinoma patients	9	10	21	26	29	38	27	16	12	7	3	2
CControl patients	0	3	23	21	32	30	28	30	14	10	4	3

Nine (9) of the carcinoma patients are barren. All the control patients are fertile. In the group of carcinoma patients, more individuals tend to have less number of pregnancies at the

rate of 1, 2 or 3 pregnancies per patient than in the control group, while on the other hand, in the control group more individuals tend to have greater number of pregnancies at the rate of 4, 5 or more pregnancies per patient than in the cancer group, a fact further illustrated graphically in fig. 5.

Births

Living Children- Carcinoma patients have a total of 535 living children against a total of 682 living children for the control. Table XIV shows the distribution of living children amongst carcinoma patients and control patients.

TABLE XIV

Distribution of Living Children Amongst 200 Carcinoma Patients (P) and 200 Control Patients (C)

Age-group of mothers (P/C)	No. of Mothers	Total	No. of Children Living		
			Patients Average/ woman	Total	Control Average/ woman
20-29	14	39	2.79	27	1.93
30-39	46	125	2.72	142	3.09
40-49	66	165	2.50	179	2.71
50 -59	39	126	3.23	137	3.51
60-69	29	68	2.34	177	6.10
70-79	6	12	2.00	20	3.33
	200	535	2.68	682	3.41

Carcinoma patients have on the average less number of living children than the control (2.68 against 3.41). But there is less variation among the age groups for the cancer patients than for the controls. Whereas the range is 1.23 for carcinoma patients, it is 4.17 among the control group. Because of this large variability in the control, the difference between the overall average is not statistically significant.

Dead Children/Stillbirths and Miscarriages

The carcinoma patients have a total of 317 dead children, 18 stillbirths and 118 miscarriages amongst them. The control patients on the other hand, have a total of 286 dead children, 8 stillbirths and 113 miscarriages amongst them. Tables XV and XVI show the age-group distribution of the total number of dead children and the total number of miscarriages amongst the carcinoma, and the control patients respectively.

TABLE XV

Distribution of Dead Children/Stillbirths Amongst 200 Carcinoma Patients (P) and 200 Control Patients (C)

Age-Group of mothers	No. of mothers	Total	No. of Dead Children		
			Patients Average/ woman	Total	Control Average/ woman
20-29	14	7	0.50	4	0.29
30-39	46	67	1.46	50	1.09
40-49	66	111	1.69	90	1.36
50-59	39	75	1.92	68	1.74
60-69	29	42	1.45	60	2.07
70-79	6	15	2.50	14	2.33
	200	317	1.59	286	1.43

TABLE XVI

Distribution of Miscarriages Amongst 200 Carcinoma Patients (P) and 200 Control Patients (C)

Age-Group of mothers P/C	No. of mothers	Total	No. of Miscarriages		
			Patients Average/ female	Total	Control Average/ female
20-29	14	1	0.07	4	0.29
30-39	46	27	0.59	26	9.57
40-49	66	24	0.36	28	0.42
50-59	39	40	1.03	31	0.79
60-69	29	21	0.72	19	0.66
70-79	6	5	0.83	5	0.83
	200	118	0.59	113	0.57

The average number of dead children per carcinoma patient is 1.59, and that per control patient is 1.43. The average number of miscarriages per carcinoma patient is 0.59 and that of the control is 0.57. These figures show that the average number of dead children per female is highest in the carcinoma patients than in the control patients. The same observation holds for the average number of miscarriages per female. The difference in each of the two ratios for the groups is not statistically significant.

Breast Feeding Pattern

Twelve (6 per cent) of carcinoma patients did not breast feed at all, 9 of the patients being barren, and the other 3 patients have lost their children soon after birth. Four (2 per cent) control patients on the other hand did not breast feed at all because they lost their children soon after birth. The remaining 188 (94 per cent) carcinoma patients, and 196 (98 per cent) control patients breast fed their children. The carcinoma patients breast fed a total of 614 children while the control patients, on the other hand, breast fed a total of 817 children.

Table XVII shows the total number of children breast fed by either the carcinoma or the control patients, grouped according to the number of years spent per woman breast feeding a child.

TABLE XVII

TOTAL NO. OF YEARS SPENT BREAST FEEDING A CHILD BY GROUPS OF PATIENTS (P)/ CONTROLS (C)

—	Total No. of Children Breast Fed		Time Spent Breast Feeding a Child	Total No. of Years Breast feeding all Children	
	(P)	(C)		(P)	(C)
	42	61	1 year	42	61
	267	384	2 years	534	768
	268	298	3 years	804	894
	36	56	4 years	5	90
Total	614	817		1529	2037
Average	3.1	4.1			

In both groups of carcinoma and control patients, women are found who spent 1 year, and up to 5 years each, breast feeding a child. There is a slight variation on the time spent breast feeding a child and percentage of women in each group of cases. The number of females, who have spent 2 years per woman breast feeding a child is

greater in the control (24 per cent) than in the carcinoma patients (19 per cent). On the other hand, the number of fmales who have spent 3 years breast feeding a child, is greater in the carcinoma patients (22 per cent) than in the control patients (18 per cent). In the series each carcinoma patient breast fed an average of 3.1 children, while each control patient breast fed an average of 4.1 children, but both the carcinoma and the control patients, spent the same average time, 2.5 years breast feeding a child.

SECTION: 2: PATHOLOGY OF BREAST CANCER IN NIGERIA

A. MACROSCOPIC FEATURES

General Features:

Malignant lesions of the breast in Nigeria present pictures of growth as variegated and rampant as the vegetations of our tropical rain forest. Inaccessibility to medical care, the far distance of the few available hospitals, fear of reality to cancer as possible cause of death, and social taboo associated with loss of breast by mastectomy, are the main factors that contribute to delay in many patients seeking medical aid. As a result, an occasional patient may present with an autoamputated breast due to breast malignant disease as shown in the photograph 1. Advanced, ulcerated, fungating lesions, usually secondarily infected, with metastasis to the axillary lymph nodes are often seen in the surgical clinics as shown in the photograph 2. Delay in seeking medical aid is equally observed in men as portrayed in the photographs 3 and 4, where the malignant lesions have ulcerated through the skin around the areola of two male breasts.

The nipple, in malignancy, may be normal and erect, levelled, depressed or destroyed by the growth as illustrated in photographs 3 and 4. Nipple retraction is often encountered with some tumours depending on the nature and site of the primary

malignant lesion. Nipple discharge can be bloody, sero-sanguineous or purulent. In pregnant women with malignancy, milk, admixed with blood, may also be expressed from the nipple.

Duration of Symptoms:

This is very difficult to determine, most of the patients having spent a considerable length of time with the native docotors treating their incurable,non-healing breast ulcers. Histories obtained from most of them are in most cases unreliable. In spite of this, the available recorded duration of symptoms of most patients are variable and ranged from 2 months to 3 years.

Location of Tumours:

Fifty-five (55) per cent of the malignant tumours affect the right breast and 45 per cent affect the left breast in the females. The reverse is true in the male patients, where 65 per cent of the lesions are located in left breastand 35 per cent in the right breast.

Bilaterality of Tumours:

Bilateral growths are seen in 7 cases. One female patient has a carcinoma in one breast and a fibroadenoma in the other breast. All the patients with bilateral neoplasia are females and no case is found in the males.

Lymphatic Spread of Tumours:

Spread to axillary lymph nodes can be unilateral or bilateral. Supraclavicular lymph nodes are invariably involved. There is in most cases associated lymphoedema of the arm on the side of the affected breasts, which in some neglected cases can be enormous as shown in phogograph 5. Wide spread metastases to most internal organs are observed in such cases.

Gross Appearances of Tumours:

Most malignant tumours are usually rather large and well circumscribed as shown in photographs 6 and 7 with a progressive extension of the growth to the axillary lymphonodes as seen in photograph 7. In some cases the tumours can massively and diffusely involve the breast tissue almost completely replacing its parenchyma, and showing cystic changes in places (photograph 8).

Nodularity of tumours with areas of haemorrhage necrosis and ulceration through the skin are common findings in the breast tumours seen locally (phograph 9).

Tethering to the skin, peau d'orange, cancer en cuirasse are commonly encountered in most breast carcinomas. Fixation to pectoral muscles and chest wall as well as their invasion by the

neoplasia are common, particularly in male breast tumours (photograph 10). From the foregoing, it is apparent that the diameters of breast tumours are variable and may range from 3 to 20 cms. or more.

B. HISTOPATHOLOGICAL FEATURES

Histological Classification:

The female and male histological types of breast carcinoma seen here in Nigeria are broadly grouped in the first instance into :-

(i) GROUP I - Neoplasms of Mammary Tissue Proper.

and (ii) GROUP II - Neoplasms of Anatomically Related Structures to the breast.

GROUP I - Neoplasms are further classified into sub-Groups as follows :-

(A) Neoplasm of Lobular Epithelial Origin (Group I, A). All the two histological types of this sub-group are diagnosed here. They are :

(1) Lobular Carcinoma in situ (Group I, A. 1)

(2) Lobular Carcinoma (invasive), (Group I, A. 2)

(B) Neoplasms of the Ductal Epithelial Origin (Group I, B). This sub-group is the largest and commonest type of all the epithelial carcinomas of the breast here. The following are its main histological types :

(1) Intraductal Carcinoma (Group I, B. 1)

(2) Intracystic Carcinoma (Group I, B. 2)

(3) Carcinoma with diffuse Fibrosis (Group I, B. 3)

(4) Circumscribed Carcinoma (Group I, B. 4)

(5) Papillary Carcinoma (Invasive) (Group I, B. 5)

(6) Colloid Carcinoma (Group I, B. 6)

(7) Medullary Carcinoma with Lympho/plasma cell infiltration (Group I, B. 7)

(a) Medullary Carcinoma with no Lympho/plasma cell infiltration (Group I, B. 7a)

*(b) Medullary Carcinoma with Polymorpho-nuclear leucocytic infiltration.

(8) Carcinoma of Breast with squamous metaplasia (Group I, B. 8)

(9) Carcinoma of Breast with osseous/cartilagenous metaplasia (Group I, B. 9)

(10) Carcinoma of Breast with sarcomatoid metaplasia (Group I, B. 10)

(11) Carcinoma of Breast with apocrine metaplasia (Group I, B. 11)

(12) Tubular Carcinoma (Group I, B. 12)

(14) Secretory Carcinoma (Group I, B. 14)

Both Signet-ring Carcinoma (Group I, B. 13) and Carcinoma

of breast with granular cells (Group I, B. 15) are not diagnosed in the series.

*(17) Carcinoma of the Breast with Composite histological structures.

(C) Neoplasms of Undetermined Epithelial Origin (Group I, C.)

The only two histological types of this sub-Group diagnosed in this series are :

(1) Lipid cell carcinoma (Group I, C. 1)

(2) Paget's disease of the Nipple (Group I, C. 4)

No case of Adenoid cystic carcinoma (Group I, C. 2) and Malignant mixed tumour of salivary gland (Group I, C. 3) are diagnosed in the series.

(D) Neoplasms Originating in Specific Mammary Connective Tissue (Group I, D.)

All the histological types of this sub-Group are found here. They are :

(1) Giant Fibroadenoma (Group I, D. 1)

and (2) Stromal Sarcoma, (Group I, D. 2)

*These sub-groups of tumours are not internationally recognised. They are included here to complete the histological types seen in Nigeria (see page 187)

GROUP II - Neoplasms of Anatomically Related Structures to the Breast. These neoplasms are further classified into the following sub-Groups :

(A) Neoplasms of Epithelial Origin (Group II, A.) (Skin and adnexa). None of the histological types of this sub-group of mammary carcinoma is diagnosed in the series. These include :

(1) Squamous cell carcinoma (Group II, A. 1),

(2) Basal cell carcinoma (Group II, A. 2),

(3) Eccrine Sweat Gland carcinoma (Group II, A. 3) and

(4) Malignant Melanoma (Group II, A. 4).

(B) Neoplasms of Non-Specific Connective Tissue Origin (Group II, B.). The only histological type of mammary malignant lesion diagnosed in this group is Liposarcoma (Group II, B. 2). Angiosarcoma (Group II, B. 1), Rhabdomyosarcoma (Group II, B.3) and Granular cell Myoblastoma (Group II, B.4) are not found in the series.

(C) Neoplasms of Lymphoreticular Origin (Group II, C.)

The histological types of this sub-group are commonly diagnosed in young female and male breast lesions here. All its histological types are diagnosed in the series. They include : Lymphosarcoma (Group II, C. 1), Reticulum cell sarcoma, Burkitt's type (Group II, C. 2) and Reticulum cell sarcoma, Non-Burkitt's type (Group II, C. 3).

C. HISTOLOGICAL EPIDEMIOLOGY OF BREAST CARCINOMA IN NIGERIA

PERCENTAGE DISTRIBUTION OF VARIOUS HISTOLOGICAL TYPES:

1. The 8 Common Histological Types in Females:

Table XVIII shows the 8 commonest histological types of female breast carcinoma, including the number of cases diagnosed for each type and their percentage of the total number of all the cases reviewed, in the descending order of their frequency.

TABLE XVIII

Histological Types of Female Breast Carcinoma
(With No. of Cases/Percentages)

Histological Type	No. of Cases	Per-centage
Medullary carcinoma, (I, B. 7)	116	26%
Carcinoma with diffuse Fib. (I, B. 3)	85	19%
Circumscribed carcinoma (I, B. 4)	52	12%
Intraductal carcinoma, (I, B. 1)	40	9%
Papillary carcinoma invasive(I, B5)	40	9%
Lobular carcinoma invasive(I, A. 2)	24	5%
Colloid carcinoma, (I, B. 6)	17	4%
Paget's disease of Nipple (I, C. 4)	16	4%

All these tumours are neoplasms of mammary tissue proper. Lobular carcinoma, invasive (I, A. 2), is neoplasm of lobular epithelial origin, and the 6th commonest tumour in the female breast Paget's disease of Nipple (I, C. 4), classified as neoplasm of undetermined origin, is the 8th commonest female breast tumour. The rest are neoplasms of ductal epithelial origin. Medullary carcinoma (I, B. 7) is the commonest histological type of all breast carcinoma in Nigeria. The second commonest is the carcinoma with diffuse fibrosis, followed by circumscribed carcinoma (I, B. 4) as the third commonest histological type. Intraductal carcinoma (I, B. 1 .) and papillary carcinoma (I, B. 5) are the 4th and the 5th commonest histological types in this series.

2. Rare Histological Types in Females:

Table XIX shows the rare histological types in female neoplasia, the number of cases and their percentages, in descending order of their frequency.

TABLE XIX

Rare Histological Types in Female Neoplasia With No. of Cases/Percentages

HISTOLOGICAL TYPE	No. of Cases	Per-centage
Reticulum cell sarcoma, Burkitt's type (II, C. 2)	10	2%
Carcinoma of breast with sarcomatoid metaplasia (I, B. 10)	9	2%
Carcinoma of breast with apocrine metaplasia (I, B. 11)	8	2%
Lobular carcinoma, in situ (A. 1)	7	2%
CCa. of breast with squamous metaplasia (I, B. 8)	5	1%
Secretory carcinoma (I, B. 14)	5	1%
Intracystic carcinoma (I, B. 2)	3	1%
Reticulum cell sarcoma, Non-Burkitt's type (II, C. 3)	3	1%
Lymphosarcoma (II, C. 1)	2	1%
Fibrosarcoma (C. 1, D. 1)	1	1%
Tubular carcinoma (I, B. 12)	1	1%
Carcinoma with osseous/cartilagenous metaplasia (I, B. 9)	1	1%
Carcinoma of breast with composite histological structures	10	2%

Reticulum cell sarcoma (Burkitt's type) is the commonest of all these rare tumours. Lymphosarcoma is also rare but does occur as a primary malignant breast neoplasm. The rest are carcinomas of the ductal epithelial origin, except lobular carcinoma in situ which is a neoplasm of lobular epithelial origin.

3. Percentage Distribution of Histological Types in Males:

Table XX shows the percentage distribution of histological types of male breast malignant neoplasia seen in Nigeria.

TABLE XX

Histological types of male breast malignant Neoplasia

Histological Type	No. of cases	Percentages
Papillary carcinoma (invasive) (I, B. 5)	9	38%
Circumscribed carcinoma (I, B. 4)	1	8%
Carcinoma with diffuse fibrosis	1	4%
Intraductal carcinoma (I, B. 1d)	3	13%
Lobular carcinoma (invasive) (A. 2)	3	13%
Coloid carcinoma (I, B. 6)	1	4%
Paget's disease of Nipple (I, C. 4)	1	4%
Reticulum cell sarcoma, Burkitt's Type (II, C. 2)	1	4%
Reticu. cell sar., Non-Burkitt's Type (II, C. 3)	1	4%
Lymphosarcoma (I, C. 1)	1	4%

When table XX is compared with tables XVIII and XIX, it becomes obvious that there is no difference between the main histological types found in male breast lesions and those found in female breas lesions. The commonest histological type of male mammary neoplasia, is papillary carcinoma, invasive. The second and the third commonest are intraductal carcinoma and lobular carcinoma, invasive.

4. Percentage Age-group Distribution of various Histological Types in Females

(a) The 8 Common Histological Types in Female:

Table XXI shows the percentage distribution of the total number of each histological type of female breast carcinoma to various age-groups.

TABLE XXI

Histological type of female Breast Carcinoma to various Age-Group

Histological Type	AGE - GROUP							
	(10)16-19 %	20-29 %	30-39 %	40-49 %	50-59 %	60-69 %	70-79 %	80-8 %
Medullary carcinoma	-	9	23	34	22	11	-	2
Ca. with diffuse fibrosis	1	7	26	36	21	10	-	-
Circumscribed carcinoma	-	-	22	42	22	11	3	-
Intraductal carcinoma	-	5	25	33	16	18	3	-
Papillar carcinoma	-	3	22	47	16	16	-	-
Lobular carcinoma	-	4	22	43	13	17	-	-
Colloid carcinoma	-	-	17	42	33	8	-	-
Paget's disease of Nipple	-	-	27	47	20	7	-	-

Fig. 6 illustrates graphically the distribution of some of the commonest female histological types of mammary carcinoma to various decades of life.

The percentage incidence of each of the eight commonest female histological types of carcinoma rises with increasing age from 16-19

age-group to reach its peak in women at 40-49 age-group and then falls toreach a lower level in women at 80-89 age-group, to a level almost comparable to that obtained in women 16-19 years of age. It is obvious that the percentage incidence of each type of breast carcinoma is lowest at the two extremes of life, in the teenage women and in the elderly women. In these two extremes of life only carcinoma with diffuse fibrosis is diagnosed in the teenage girls between 16-19 years of age, and only medullary carcinoma in the elderly women between 80-89 years of age.

20-29 Year Age-Group Women: Medulary, intraductal, papillary and lobular carcinomas commence to afflict the female breasts in their early twenties. These carcinomas along with carcinoma with diffuse fibrosis, are the main malignant tumours of the young women of this age-group. Medullary carcinoma followed by carcinoma with diffuse fibrosis and intraductal carcinoma are the commonest histological types of carcinomas occurring in such young women. Lobular carcinoma, invasive and papillary carcinoma do occur but are of proportionately lower percentage incidence than the rest.

30-39 Year Age-group Women: Circumscribed carcinoma, colloid carcinoma, and Paget's disease of Nipple do not appear

to afflict young Nigerian women in their teens and twenties, but appear to increase steeply in older females from their thirties onwards, the latter being the period at which carcinomas commence to afflict the male breast in this community. Paget's disease of nipple, carcinoma with diffuse fibrosis, and intraductal carcinoma are the commonest histological types of breast carcinoma found in this age-group, followed by medullary carcinoma, papillary carcinoma, circumscribed carcinoma and lobular carcinoma invasive. The percentage incidence of colloid carcinoma is proportionately low in women of this age-group.

40-49 Year Age-group Women: All the eight common histological types of carcinoma appear to have their peak percentage incidence in women at this period. The commonest types usually found at this age-group are papillary carcinoma, Paget's disease of nipple followed by lobular carcinoma, invasive circumscribed carcinoma and colloid carcinoma. Carcinoma with diffuse fibrosis, medullary carcinoma and intraductal carcinoma have proportionately low percentage incidence in these women.

50-59 Year Age-group Women: The percentage incidence of all the histological types gradually fall in women at this age-group. Here colloid carcinoma has the highest percentage incidence, followed by circumscribed carcinoma, medullary carcinoma, carcinoma with diffuse fibrosis and Paget's disease of nipple. The percentage incidence of papillary carcinoma, intraductal carcinoma and lobular carcinoma invasive is proportionately low in women of this age-group.

60-69 Year Age-group Women: The percentage incidence of all histological types of breast carcinoma has fallen appreciably at this age-group. The commonest histological types encountered are intraductal carcinoma, lobular carcinoma invasive and papillary carcinoma. These are also the commonest histological types of breast carcinoma found in the male breasts of this age-group. Circumscribed carcinoma and medullary carcinoma and carcinoma with diffuse fibrosis, colloid carcinoma and Paget's disease of nipple have also low percentage incidence in this age-group.

70-79 Year Age-group Women: Only circumscribed carcinoma and intraductal carcinoma are diagnosed in the series, and in the 80-89 Year Age-group Women, only medullary

carcinoma is diagnosed in two elderly women, aged 80 years respectively.

TABLE XXII

(b) THE RARE HISTOLOGICAL TYPES IN FEMALES

Histological Type	(10)12-19	20-29	30-39	40-49	50-59	60-69	69-79	80-89
Burkitt's	50%	40%	50%	-	-	-	-	-
Ca. with squamous metaplasia	-	-	20%	-	40%	40%	-	-
Ca. with sarcomatoid metaplasia	-	40%	40%	20%	-	-	-	-
Ca. with apocrine metaplasia	-	-	33.33	16.67	16.67	16.67	16.67	-
Lobular Ca. in situ	-	-	-	-	-	-	-	-
Secretory carcinoma	-	50%	50%	-	-	-	-	-
Lipid cell carcinoma	-	-	100%	-	-	-	-	-
Lymphosarcoma	-	-	-	-	-	-	-	-
Tubular carcinoma	-	100%	-	-	-	-	-	-
Liposarcoma	-	-	100%	-	-	-	-	-
Malignant giant fibroadenoma	-	100%	-	-	-	-	-	-
Carcinoma with osseous/cartilagenous metplasia	-	-	100%	-	-	-	-	-

Table XXII shows that between 10-19 years of age, reticulum cell sarcoma, Burkitt's type, is the only type of malignant lesion that appears to afflict both the female and male breasts of this age-group. Between 20-29 years of age, carcinoma with squamous metaplasia, secretory carcinoma, tubular carcinoma and malignant giant fibroadenoma are the commonest types of rare carcinoma diagnosed in women of this age-group. Most rare breast tumours are commonly diagnosed in 30-39 year age-group women. From 40 years of age onwards all types of rare tumours, are extremely rare in women. Only 1 case of Burkitt's lymphoma is diagnosed in a 35-year old woman, who was lactating. Burkitt's lymphoma, and other types of sarcomas are the disease of the very young in Nigeria, and are rarely seen in female breasts after the menopause.

TABLE XXIII

(c) PERCENTAGE AGE-GROUP DISTRIBUTION OF HISTOLOGICAL TYPES IN MALES

Histological Type	Age - Group (10)	15-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89
Papillary Ca.	-	-	13%	13%	65%	13%	-	-
Lobular Car. (invasive)	-	-	-	-	-	75%	25%	-
Intraductal Ca.	-	-	-	-	-	-	50%	50%
Circumscribed carcinoma	-	-	-	100%	-	-	-	-
Ca. with diffuse fibrosis	-	-	-	-	-	-	100%	-
Paget's disease of Nipple	-	-	-	-	-	-	100%	-
Colloid carcinoma	-	-	100%	-	-	-	-	-
Burkitt's	100%	-	-	-	-	-	-	-
Reticulum cell sarcoma, Non-Burkitt's type	-	-	100%	-	-	-	-	-
Lymphosarcoma	100%	-	-	-	-	-	-	-

Table XXIII shows that between 10-29 years of age, male breast carcinoma did not occur. Between 30-39 years of age, papillary carcinoma and colloid carcinoma are the two most common histological types of breast carcinoma that appear to be diagnosed in themale breast lesions. Between 40-49 years of age, papillary carcinoma (invasive) appears to be the only common histological type of male breast carcinoma in this community. Only one case of circumscribed carcinoma was diagnosed in a male of 40 years of age. Papillary carcinoma is the predominant histological type in males between 50-59 years of age. Lobular carcinoma (invasive) intraductal carcinoma, carcinoma with diffuse fibrosis are variously diagnosed in males 60-80 years of age and above. Burkitt's lymphoma and lymphosarcoma are the diseases of the young males, and have not been diagnosed in the breast lesions of older men in this community.

Average Ages of Various Histological Types in the Female:

Table XXIV shows the average, median and modal ages of the various histological types.

TABLE XXIV

AVERAGE AGE OF THE EIGHT COMMON HISTOLOGICAL TYPES OF BREAST CARCINOMA IN FEMALES

Lesions	Average Age (yrs.)	Median Age (yrs.)	Modal Age (yrs.)
Medullary carcinoma	42.7	43	45.5(41-50)
Ca. with diffuse fibrosis	43	43.5	43.4 (41-50)
Circumscribed carcinoma	44.3	43.8	43 (41-50)
Intraductal carcinoma	43	41.0	40 (31-40)
Papillary carcinoma	42.1	42.3	42.3 (41 -50)
Lobular carcinoma	45.5	45	45 (31-40)
Colloid carcinoma	48	45	45.5 (41 -50)
Paget's disease of Nipple	44	40	40 (31-40)

Medullary carcinoma and papillary carcinoma on the average are the carcinomas of the young women in this community with an average age of 42.7 years and 42.1 years respectively. These are followed by carcinoma with diffuse fibrosis and intraductal carcinoma, each with an average age of 43 years. Circumscribed carcinoma and

Paget's disease of the nipple, with an average age of 44.3 and 44 years respectively, appear on the average to occur in women 1.6 years older than women with medullary carcinoma. Lobular carcinoma and colloid carcinoma are definitely the diease of the older females with average ages of 45.5 and 48 years respectively. An average woman with lobular carcinoma (invasive) is 2.8 years older than average woman with medullary carcinoma, while an average woman with colloid carcinoma is 5.3 years older than an average woman with medullary carcinoma. Medullary carcinoma, papillary carcinoma, carcinoma with diffuse fibrosis, circumscribed carcinoma and colloid carcinoma have a common modal age of 41-50 years, while intraductal carcinoma, Paget's disease of the nipple and lobular carcinoma, invasive have a common modal age of 31-40 years.

General Microscopic Features:

Nearly all the histological types of breast malignant neoplasia reviewed in this current study are invasive. These tumour types are variously encountered with haemorrhagic, coagulative or liquefaction necrosis. The main host cellular reaction to the presence of these tumours that are often encountered with are lymphocytes, plasma cells, histiocytes, polymorphonuclear leucocytes and eosinophils. The dominance of cellular host reaction varies much with the

histological type of tumour, but in general, most tumours have abundant lymphocytic infiltration. Most male neoplasia show marked stromal desmoplasia but in general, stromal fibrosis can be abundant or scanty depending on the tumour type. Thus in carcinoma with diffuse fibrosis, stromal fibrosis in some cases may be abundant while in others moderate or scanty. Hyalinisation of the tumour stroma is often associated with postmenopausal carcinoma. In some cases, mammary ductal and vascular walls are thickened by fibrosis that may be markedly hyalinised with complete obliteration of their lumina. Carcinoma with lymphatic and venous tumour emboli are common in most cases ecountered in Nigeria.

Microcalculi and Breast Carcinoma:

Microcalculi are often seen in most breast carcinomas associated with fibrocystic disease of the breast. Thus, they are a common finding in intraductal carcinoma, and other histological types that have definite relationship to this benign lesion of the breast. They are often seen in breast tissue adjacent to areas of an in situ lobular carcinoma, and in areas of necrosis of medullary carcinoma, circumscribed carcinoma, invasive papillary carcinoma, and carcinoma with diffuse fibrosis. With the latter, the walls of the mammary ducts are often thickened, hyalinised and sometimes calcified. The walls

of medium sized arteries supplying such a tumour may be sclerosed, hyalinised and calcified, particularly in elderly atrophic breasts with certain histological types of carcinoma. In carcinoma of breast with osseous/cartilagenous metaplasia, areas of calcification that may progress to bone formation is usually diagnostic. These facts are illustrated in figs. 7 and 8.

Depigmentation Phenomenon and Breast Carcinoma in Nigeria:

In the normal skin of a Nigerian, the melanocytes of the basal layer of the epidermis contain non-aggregated melanin granules. The cells of the malpighian layer are also sparsely pigmented. When either male or female breast is afflicted by a large carcinoma, the area of the skin overlying the tumour is stretched and oedematous, presenting peau d'orange appearance. It becomes light brown in colour in contrast to the normal dark coloured skin remote from the tumour.

Two different states are observed microscopically in the epidermis. Firstly, when the tumour is deeply situated in the breast parenchyma, and is remote from the epidermis the latter remains normally pigmented fig. 9. Secondly, as the peripheral border of the advancing tumour is approaching the dermo-epidermal juction, the epidermis shows moderate or marked hyperkeratosis and acanthosis with the elongation of the rete pegs. Melanin granules become

aggregated, and diffusely dispersed in the cytoplasm of all the squamous cells of the malpighian and basal layers. Excessive spongiosis causes some centrally placed cells in malpighian layer to burst, liberating their melanin granules. The latter becomes coalesced to form homogenous dark melanin lakes as shown in focal areas in the malpighian layer in the fig. 10. In the upper dermis, just below the basement membrane of the epidermis are seen macrophages laden with melanin granules that have diffused out of the epidermal cells, aggregates of lymphocytes, plasma cells and occasional eosinophils, as shown in fig. 11. These cells are seen interposed between the edge of the advancing tumour cluster and the epidermis. When the tumour has advanced to the epidermis, having broken through the cellular infiltrate, the epidermal cells become almost completely depigmented, thus resembling the epidermis of the skin of a normal caucassian (fig. 12). Under this depigmented state the epidermis is seen to be invaded by nests of malignant cells as shown in fig. 13. Some of the invading malignant tumour cells may be seen with engulfed melanin granules diffusely scattered in their cytoplasm, as shown in fig. 14, a histological appearance that may resemble an intra-epidermal melanoma. In some cases histiocytes laden with phagocytosed melanin granules migrate deeply into the

stroma of the tumour cells as shown in fig. 15. In certain cases, some of the tumour cells are seen with engulfed melanin pigments scattered in their cytoplasm. This is not a rule, as in many tumours no phagocytosed pigments are found in the malignant cells, but the lymph nodes draining such tumours are often packed with melanin-laden histiocytes as shown in fig. 16.

This type of depigmentation phenomenon of the epidermis is often encountered with very large mammary carcinomas such as medullary carcinoma, invasive papillar carcinoma, circumscribed carcinoma and large lobular carcinoma (invasive), which readily expand massively to involve the overlying skin. This is a localised phenomenon. It seems that the loss of the pigment may be an associated phenomenon but not necessarily a precursor of epidermal invasion. There is no evidence that melanin is "protective" and loss of pigment may be due to the increased vascularity and inflammatory reaction associated with the tumour.

Microscopic Vascular Spread of Various Histological Types:

Both lymphatic and venous tumour emboli are commonly seen histologically in most tumours. The lymphatic vassels are often dilated with the tumour mass lying centrally in what appears like empty spaces. Once this is observed, the associated regional lymph

node is invariably malignant. Venous invasion seen in some cases often leads to disseminated systemic metastases. The percentage distribution of 104 (female) and 4 (male) metastatic lymph nodes resulting from various histblogical types of primary female and male mammary carcinoma are shown in Tables XXV and XXVI, below :

TABLE XXV

FEMALE LYMPH NODE METASTASES

Histological Type	Percentage(%)
Carcinoma with diffuse fibrosis	32%
Medullary carcinoma	22%
Circumscribed carcinoma	18%
Papillary carcinoma (invasive)	18%
Lobular carcinoma (invasive)	5%
Intraductal carcinoma	4%
Colloid carcinoma	1%

TABLE XXVI

MALE LYMPH NODE METASTASES

Histological Type	Percentage(%)
Papillary carcinoma (invasive)	50%
Circumscribed carcinoma	17%
Lobular carcinoma (invasive)	17%
Ca. with apocrine metaplasia	17%

Carcinoma with diffuse fibrosis is the most aggressive histological type that commonly gives rise to lymphatic tumour emboli in the breast primary, and there is invariably associated reginnal lymph node metastasis. It accounts for 32 per cent of all the female malignant lymph nodes examined. Colloid carcinoma is a slower growing breast carcinoma and least likely to metastasise. It accounts for only one per cent of all the metastatic lymph nodes. Papillary carcinoma invasive, the commonest male breast carcinoma, is rather aggressive in the male patients. It accounts for 50 per cent of all the male metastatic lymph nodes, and only 18 per cent in the female. Figs. 17 and 18 show grossly dilated lymphatics stuffed with islets of malignant tumour emboli.

SECTION 3: RELATIONSHIP OF BREAST BENIGN LESIONS TO MALIGNANT BREAST NEOPLASIA

It has been shown that malignant tumours are commoner lesions than benign breast masses in Nigeria. This may be because most patients do not complain of benign tumours - although they may be present. The most common female benign processes encountered in Nigeria are fibroadenomas (16 per cent), fibrocystic disease (11 per cent) and giant fibroadenoma (1 per cent).

Fibroadenoma and Breast Carcinoma:

Ten (10) of the 183 cases of fibroadenoma reviewed had bilateral fibroadenoma, and one 46 year old patient had fibroadenoma in the left breast and a carcinoma in the right breast. All the patients had simple excision of their breast lumps, with exception of the 46 year old lady who had right mastectomy for carcinoma, and 'lumpectomy' for her fibroadenoma. Histologically the lesions commonly seen here are mixture of pericanalicular and intracanalicular fibroadenoma. Only one case of all the patients reviewed had superimposed malignant change in her benign fibroadenoma. This is a case in a 20 year old woman who presented with growing lump of the

breast. She had radical mastectomy. The histology shows an intracanalicular and pericanalicular fibroadenoma with pale oedematous rather sparsely cellular stroma (fig. 19). Most of the epithelial cells are secretory. In other areas the ductal epithelial cells appear hyperplastic, dysplastic and frankly malignant (fig. 20). They form glandular spaces which are rather pleomorphic and embedded in scanty stroma. The cells have abundant secretions in their cytoplasm and in the glandular spaces. Figure 21 shows hyperplastic and dysplastic areas in the fibroadenoma. In the lower portion of the figure the malignant epithelial cells have formed glandular spaces, enlarging and deforming the normal mammary lobular architecture. Secretions are present in the ducts and in the glandular spaces of the malignant cells. Figure 22 shows the high power view of an area of such a carcinoma. Most of the malignant cells are distended by secretion which makes the cytoplasm of the cells appear vesicular. The enlarged nuclei are hyperchromatic and show prominent chromatin granules and nucleoli. Mitotic figures are haphazardly scattered in the malignant cells. These appearances do suggest a diagnosis of secretory (juvenile) breast carcinoma, but one however, needs evidence of metastasis of this type of tumour to really prove malignancy; but in this retrospective study there was no such evidence.

Malignant Giant Fibroadenoma:

Only one case of malignant giant fibroadenoma was recorded in the Cancer Registry. The patient was a 45 year old woman who presented with massive tumour of the breast that was excised. The histology shows malignant giant fibroadenoma with dilated cystic spaces, some of which are compressed into slits lined by flattened epithelial cells (fig. 23). The stroma consists maily of malignant fibroblasts with plump nuclei showing prominent chromatin granules. The nucleoli are prominent in some places. The malignant spindle cells are arranged in parallel streams with rather scanty lympho-plasma cell infiltration. Areas of necrosis demarcated from viable sarcomatous tumour cells by lympho-plasma cell infiltration are also observed in the tumour (fig. 24).

Gynaecomastia and Breast Cancer:

There were 41 lesions of the male breast in the Cancer Registry. Twenty-four (58 per cent) of these were malignant tumours, 8 (19 per cent), gynaecomastia, and the rest (22 per cent) were due to chronic non-specific inflammations of the breast. The eight patients with gynaecomastia were aged 13, 21(2), 25(2), 31 and 38 years respectively, the remaining two being recorded as adults. Histologically all the sections show marked stromal desmoplasia with proliferation of ducts

without development of gland fields, see figure 25, where groups of dilated ducts are scattered in the remarkably fibrous stroma. In some cases, attempts at abortive glandular lobule formation by the proliferating ducts are observed (fig. 26). The lining epithelium of the ducts sometimes show moderate to marked papillomatesis. Aprocrine metaplasia of the lining ductal epithelial cells may occur in some cases, (fig. 27). Figure 28 shows an intraductal paillary carcinoma in one of the sections obtained from the excised breast lesion diagnosed as gynaecomastia in a 38 year old male patient. Here the tips of the finger-like papillary processes have fused in places to form the characteristic cart-wheel pattern which Haagensen (1971), had described as one of the characteritics of intraductal papillary carcinoma. Many nests of coreless papillae due to sectioning are present in the central portion of the duct. There is no invasion of the surrounding fibrous stroma in all the sections examined. This is the only malignant lesion present in all the cases of gynaecomastia reviewed. Papillary carcinoma of course, is the commonest histological type of male breast cancer in Nigeria. It is often associated with marked stromal fibrosis. Most of the papillary carcinomas seen here are invasive and it is impossible in a review of this nature, with just this one example, to prove any real relationship between gynaecomastia and carcinoma.

Relationship of Benign Fibrocystic Disease to Malignant Breast Neoplasia:

Slides of 420 patients operated upon for breast carcinoma are studied for evidence of associated fibrocystic disease of the breast. Ninety-nine (23.8 per cent) of the cases are found to have benign fibrocystic disease in the adjoining breast tissue. In order to determine whether there is an association between fibrocystic disease and breast carcinoma, the data obtained from studying the annual age distribution of 151 patients with fibrocystic disease alone (X_1), 99 patients with carcinoma and associated fibrocystic disease (X_2) and 639 patients with carcinoma only (X_3), including the associated histological types of breast carcinoma, are analysed.

TABLE XXVII

ANNUAL DISTRIBUTION OF THE THREE CASE TYPES

Year	X_1 Cystic Disease only	X_2 Cystic Disease with Cancer	X_3 Carcinoma only
1960	0	1	27
1961	12	0	17
1962	7	1	31
1963	6	1	44
1964	6	4	48
1965	1	4	53
1966	0	3	41
1967	4	2	33
1968	3	7	36
1969	9	5	41
1970	26	10	53
1971	20	11	50
1972	13	18	50
1973	20	7	44
1974	17	10	39
1975	9	15	39
TOTAL :	151	99	639

Table XXVII above, shows the annual distribution of patients with (1) fibrocystic disease alone, (X_1), (2) patients with fibrocystic

disease associated with carcinoma, (X_2) and (3) patients with carcinoma only, (X_3) collected during the 16 year period of this study. The average annual incidence of fibrocystic disease alone (X_1) is 9.4, that of fibrocystic disease with carcinoma (X_2) is 6.2, and that of carcinoma alone (X_3), is 38 cases.

Figure 29 shows in graphic form the annual distribution patterns of fibrocystic disease alone (X_1), (2) cystic disease associated with carcinoma (X_2) and (3) carcinoma alone (X_3). Figures 30, 31 and 32 show the scatter diagrams of the annual distribution of each of the three case types: (1) fibrocystic disease only (X_1) plotted against fibrocystic disease associated with carcinoma (X_2); (2) fibrocystic disease only (X_1) plotted against carcinoma alone (X_3); and (3) fibrocystic disease associated with carcinoma (X_2) plotted against carcinoma alone (X_3). The three case-types appear to follow a similar linear pattern. Hence for each pair of the three case types, simple correlation coefficient is calculated. The results are shown in Table XXVIII, below:

TABLE XXVIII

CORRELATION COEFFICIENT(r)* OF CASE-TYPES

Serial No.	Case Types	Value of (r)*
1.	X_1 and X_2	0.52
2.	X_1 and X_3	0.32
3.	X_2 and X_3	0.55

For a sample of 16 years, only the correlation coefficient of 0.52 obtained for the pair (1) fibrocystic disease alone (X_1) and fibrocystic disease associated with carcinoma (X_2), and 0.55 obtained for the pair (3) fibrocystic disease associated with carcinoma (X_2) and carcinoma alone (X_3), are significantly different from zero at 95 per cent level. Hence the conclusion is that there is some evidence of a positive linear association between (1) firbocystic disease alone (X_1) and fibrocystic disease associated with carcinoma (X_2), and also between (2) fibrocystic disease associated with carcinoma (X_2) and carcinoma alone (X_3).

Relationship between Fibrocystic Disease, Carcinoma and Age:

Table XXIX shows the Age-group distribution pattern of patients with fibrocystic disease only (X_1) and patients with fibrocystic disease associated with carcinoma in the same breast lesion (X_2).

TABLE XXIX

AGE-GROUP DISTRIBUTION

Lesion	Age-Group					
	11-20	21-30	31-40	41-50	51-60	above 60
Cystic disease only	20	45	36	17	6	0
Cystic disease + carcinoma	0	11	28	29	7	5
TOTAL :	20	56	64	46	13	5

In order to test the assumption that there is some association between these two diseases and age, the X^2 test (chi square test), is used. On the basis of no association, a value of 39 is obtained for X^2 4(i.e. chisquare with 4 degrees of freedom). If this assumption is true, there will be a 1 in 1,000 chance of obtaining X^2 4 as high as 18.47. Since the value, 39 obtained here is even higher than 18.47,

then there is an even a smaller chance of getting such a distribution by accident. Thus the assumption of no association is rejected, and it is concluded that there is a very strong evidence that fibrocystic disease alone (X_1) and cystic disease associated with carcinoma (X_2) are related to age.

Histological Types of Cancer Associated with Fibrocystic Disease:

Table XXX shows the various histological types of breast carcinoma found to have associated fibrocystic disease in the neighbouring breast tissue.

TABLE XXX

VARIOUS HISTOLOGICAL TYPES OF BREAST CANCER WITH CYSTIC DISEASE

Histological Type	No. of Cases	No. with Cystic Disease	Percentage
Intraductal carcinoma	31	27	67%
Lobular carcinoma	21	14	67%
Medullary carcinoma	118	32	27%
Papillary carcinoma	54	12	22%
Carcinoma with diffuse fibrosis	64	13	20%
Circumscribed carcinoma	73	14	19%
Colloid carcinoma	17	1	6%

The histological type of breast carcinoma most commonly associated with fibrocystic disease in Nigeria is intraductal carcinoma. This accounts for 67 per cent of all the intraductal carcinomas in general. Intraductal carcinoma is a carcinoma of multicentric origin that usually consists of intraductal solid, intraductal comedo, and intraductal papillary carcinoma, singly or in combination, and most usually with invasion of the surrounding breast parenchyma. The second in the series is lobular carcinomas, both in situ and invasive types.

The in situ form is always found in areas of cystic disease. Medullary carcinoma is the third type of breast carcinoma found in the series. Papillary carcinoma, invasive, is also most often associated with cystic disease. Carcinoma with diffuse fibrosis, the third commonest histological type of breast carcinoma in Nigeria, but the commonest histological type of breast cancer in Europe and America, Davis, Simons and Davis (1964), is the fifth commonest histological type of carcinoma found to be associated with cystic disease of the breast here.

Table XXXI compares the peak and average age incidence of patients with (1) fibrocystic disease alone (X_1), (2) fibrocystic disease associated with carcinoma (X_2), (3) patients with carcinoma alone (X_3) and (4) those obtained for various histological types of breast carcinoma.

TABLE XXXI

PEAK AND AVERAGE AGE INCIDENCE OF VARIOUS HISTOLOGICAL TYPES & CYSTIC DISEASE

Lesion	Peak Incidence (years)	Average Age (years)
Cystic disease alone	21-40	31
Cystic disease + Carcinoma	31-50	41
Carcinoma alone	35-60	43
Intraductal carcinoma	31-50	43
Lobular carcinoma	31-50	45
Medullary carcinoma	41-50	42.7
Papillary carcinoma	41-50	42.1
Carcinoma with diffuse fibrosis	31-50	43
Circumscribed carcinoma	31-50	44.3
Colloid carcinoma	41-50	48.0

The average age of 31 years obtained for patients with fibrocystic disease alone (X_1) is 10 years lower than the average age of 41 years obtained for patients with fibrocystic disease associated with carcinoma. The latter group of patients on the average are only two years younger than females with breast carcinoma in general,

whose average age is 43 years. When the average ages of patients with various histological types of breast carcinoma are considered, it is observed that the average age of the patients with fibrocystic disease associated with carcinoma is somehow comparable to the rest, all the patients being in their early menopausal period. Average ages tend to hint at the realities of age distribution and incidence patterns of carcinoma. Hence the peak age incidence of patients with fibrocystic disease associated with carcinoma is observed to be the same as that of patients with intraductal carcinoma, lobular carcinoma, carcinoma with diffuse fibrosis and circumscribed carcinoma. These histological types of carcinomas are the most common types usually associated with fibrocystic disease here. The peak age incidence of patients with medullary carcinoma is greater than those with fibrocystic disease associated with carcinoma. Patients with colloid carcinoma which is a slow growing tumour, on the average, are usually postmenopausal. This type of carcinoma is seldom associated with fibrocystic disease, the latter condition being seldom found in postmenopausal women.

SECTION 4: SOME SPECIAL HISTOLOGICAL TYPES OF BREAST CARCINOMA IN NIGERIA

A - LOBULAR CARCINOMA, WITH SPECIAL EMPHASIS ON MALE LOBULAR CARCINOMA

Lobular carcinoma is one of the 8 commonest histological types of breast carcinoma encountered in Nigeria. It accounts for 5 per cent of all the malignant mammary neoplasia in the female and 13 per cent in the male. It consists of two histological types :

(a) Lobular carcinoma in situ (Group I, A. 1)

(b) Lobular carcinoma (invasive) (Group I, A. 2).

Lobular Carcinoma In Situ:

All the 7 female cases in the series are incidentally discovered on reviewing histological cases diagnosed as benign mammary lesions. They are all associated with benign fibrocystic disease of the breast. The youngest female patient with this disease is aged 18 years, and the oldest 42 years. Figure 33 is a photomicrograph of a section obtained from one of such lesions. The upper part of the photomicrograph shows an enlargement of the mammary lobule involved by occult lobular carcinoma in situ. The terminal ducts are solidly stuffed with plump epithelial cells. Contrast this lobule with the lobule below showing an area of adenosis in fibrocystic disease. Figure 34

is a higher power view of the same lesion, showing the uniform malignant cells that have lost cohesion and polarity. Their nuclei appear hyperchromatic and show little variation in size. Some of the malignant cells do secrete mucin that imparts vacuolated appearance to their cytoplasm. No lobular carcinoma in situ is seen in association with the eight cases of gynaecomastia reviewed.

Lobular Carcinoma, (Invasive):

Twenty-one female and 3 male patients in the series have lobular carcinoma, invasive. The average age of females with this type of carcinoma is 45.5 years, their median age 45 years, and their modal age is also 45 years. The youngest female patient with lobular carcinoma is 26 years, and the oldest, 65 years, of age. Two of the male patients are aged 60 years each, and the third patient is 75 years of age.

Histologically, invasive lobular carcinoma is usually multifocal in origin, and presents a variety of patterns in both female and male lesions. In some cases, the small malignant uniform cells may be solely arranged in nodules/acini without any associated lobular carcinoma in situ being present in any other section of the tumour. Such a tumour may be heavily or moderately infiltrated by lympho-plasma cells (fig. 35). In other types of invasive lobular carcinoma, the small uniform malignant cells form broad and

enlongated sheets with anastomosing bands. The stroma of such tumours are often scanty but may be mucinous with little or no lymphoplasma cell infiltration, (fig.36). The malignant cells of this variant of invasive lobular carcinoma may sometimes show moderate mitosis (fig. 37).

Another histological pattern often exhibited by invasive lobular carcinoma seen here is the one in which the small uniform cells form single line of invasive cells. This is the classical Indian file pattern of invasive lobular carcinoma. This latter pattern is often seen in combination with nodular/acinar pattern of invasive lobular carcinoma. In fig. 38, the Indian file pattern on the left, is seen in combination with the nodular/acinar pattern on the right. There is no fibrous band separating the two patterns which appear to emerge in continuity.

Apocrine metaplasia may sometimes occur in some invasive lobular carcinomas. Under such conditions, the small uniform malignant cells, arranged in anastomosing sheets or nodules (fig. 39) will have granular acidophilic cytoplasm. In some areas of such tumours, the malignant cells may be seen extruding their cytoplasm into cystic cavities as snouts projecting from the medial poles of the cells (fig. 40). In such invasive lobular carcinoma the malignant

cells may be arranged in syncytial sheet with abundant lympho/plasma cell infiltration in intimate relationship with the malignant cells (fig.41). This may mimick the typical syncytial type of medullary carcinoma, but the malignant cells in invasive lobular carcinoma, unlike the malignant cells of the latter, are small and have uniform nuclei that show little or no mitosis. Lastly in some breast carcinomas, invasive lobular carcinoma may be found in combination with in situ lobular carcinoma. The regional lymph node metastasis may exhibit the Indian file pattern alone, or the Indian file pattern in combination with nodular/acinar pattern or the latter pattern only (fig.42).

Clinical Features:

The biological behaviour of invasive lobular carcinoma seen here is well portrayed in a case of a 60-year old man as follows : On 24th of April, 1973 at 7.00 a.m., a 60-year old man was admitted in the casualty department of the University College Hospital as an emergency. He had history of persistent cough, breathlessness and weight loss of about 3 months duration. On examination he was found to be an emaciated elderly man, obviously in respiratory distress. He had had a diffuse enlargement of the left breast which was diagnosed clinically as gynaecomastia. There was left axillary lymph adenopathy. Straight

chest X-ray revealed diffuse mottling and haziness of both pulmonary parenchyma. There was associated bilateral pleural effusion. A radiological diagnosis of millary tuberculosis, with massive bilateral pleural effusion, was made tentatively. A thoracotomy was performed on the left side of the chest, and multiple miliary nodular lesions were found all over the pleural surfaces of the lung and the diaphraghm. Biopsies were taken from the lung, diaphraghm and from the breast lesion. Post operatively his condition deteriorated rapidly and he died the same day. No autopsy was performed.

Macrocopic Features of the Biopsy:

The breast biopsy weighed 5gm., and measured 2.5 x 3 x 1cm. Its cut surface was homogeneous and greyish-white in colour. It was firm and rubbery in consistency and parted a gritty sensation to the cutting knife. The lung biopsy was a black tissue containing multiple greyish-white firm nodules up 2.5cm. in their greatest diameter. The diaphraghmatic biopsy was a small irregular tissue, greyish-white in colour, and firm in consistency. It cuts with gritty sensation to the knife.

Microscopic Features - Breast Biopsy:

The mammary ducts are hyperplastic and cystically dilated in places, the stroma showing marked desmoplasia. At one part of a

secition two dilated ducts are seen stuffed with malignant uniform small cells showing slight variation in size of their hyperchromatic nuclei. A few malignant cells show vacuolated cytoplasm due to mucin secretion (fig.43). These are areas of in situ lobular carcinoma as defined by Warner (1969). The two dilated ducts are separated from each other by a fibrous stroma that has undergone hyalinisation in places and moderately infiltrated by lympho-plasma cells. In another area, (fig. 44), small uniform cells, arranged in nodules/acini, are seen surrounding a dilated duct lined by hyperplastic epithelial cells. The malignant cells show centrally placed hyperchromatic nuclei with slight variation in size. Moderate mitosis can be seen. The cytoplasm of most of the individual cells are vacuolated with sialomucin. This tumour pattern has emerged imperceptibly to areas where the malignant cells show the single line of invasive cells, the Indian file pattern of invasive lobular carcinoma, which has completely replaced the mammary parenchyma (fig. 45).

Mircroscopic Features - Lung Biopsy:

There is intestital congestion of the alveolar walls with moderate oedema of the aveolar air spaces. The media of the pulmonary blood vessels are hypertrophied. Nodules of uniform tumour cells are seen packed around the tunics externa of some of the thickened pulmonary

vessels, (fig.46). Similar nodules and nests of tumour cells are seen distending the alveolar air spaces, the walls of which are disrupted in places (fig.47). These tumour nodules are similar to those found in the breast lesion. The thickened fibrotic pleura, and the diaphraghm are infiltrated by similar malignant nodules found in the lungs (fig.48).

The histological diagnosis here is carcinoma in situ, in combination with lobular carcinoma (invasive) of the left breast, with metastases to the lungs, pleura and diaphraghm. From the above, it is obvious that lobular carcinoma, when invasive, may give rise to wide spread systemic metastases.

B-- MEDULLARY AND CIRCUMSCRIBED CARCINOMAS

Medullary Carcinoma (Group I, B.7):

This is the commonest histological type of breast carcinoma encountered in Nigeria. It accounts for 26 per cent of all the malignant mammary neoplasia, almost all occuring in the premenopausal and menopausal females. 66 per cent of this tumour are found in women aged between 20-39 years; 34 per cent in women aged 40-49 years, and 35 per cent in postmenopausal women between 50-89 years of age.

Macroscopic Features:

Medullary carcinomas in general, are well circumscribed tumours that have a tendency to grow very large, and undergo either coagulative, haemorrhagic, or liquefaction necrosis with cystic formation. All these degenerative changes may be found in combination in a tumour. In neglected cases they may easily ulcerate through the skin as fungating masses. Their cut surfaces are bulging, friable and fleshy. They are greyish-white or tan-brown in colour as a result of old haemorrhage. In some cases, where dystrophic calcification has occurred, they may impart a gritty sensation to the cutting knife. Their diameters do vary a great deel, and may range from 5cms. to 20cms.

These tumours have a tendency to rapid growth with almost complete destruction of the surrounding breast tissue. Vascular invasion with regional lymph node metastasis is also quite commonly seen in medullary carcinoma.

Histological Features:

Histologically, medullary carcinomas found here are typical syncytial type as defined by Ridolfi, Rosen, Porta, Kinne and Mike (1977). They are usually composed of malignant epithelial cells that are poorly differentiated, have abundant cytoplasm that may be vacuolated. The nuclei are large, hyperchromatic, and vesicular. The nucleoli are large and prominent. The syncytial malignant cells are ovoid to polygonal in shape with indistinct cellular borders. The cells do not form structures or glands. Bizarre mitosis are common. Bizarre tumour giant cells are commonly found in most medullary carcinomas, and in some cases, tumour giant cells may be the only cellular component of such carcinomas.

Medullary carcinomas, depending on their cellular components may be broadly divided into two types :

(a) Typical syncytial medullary carcinoma.

and (b) Medullary carcinoma composed mainly of giant tumour cells.

These two cellular types may occur in combination. Squamous metaplasia may on occasions be observed in them. Most medullary carcinomas are distinguished by massive lympho-plasma cell infiltration as the main host cellular reaction to their presence. But quite a few of them in Nigeria, are infiltrated by abundant polymorpho-nuclear leucocytes and moderate eosinophils. Depending therefore, on the type of predominant host cellular reaction to their presence, medullary carcinomas may be further classified into :

(a) Medullary carcinoma with lympho-plasma cell infiltration. (Group I, B. 7a)

(b) Medullary carcinoma with polymorpho-nuclear leucocytic infiltration. (Group I, B. 7b)

and (c) Medullary carcinoma, with neither lympho/plasma cell nor polymorpho-nuclear Leucocytic infiltration (Group I, B. 7c).

Any of the above types can be composed either of typical syncytial type alone, or of tumour giant cells, or of these two types in combination.

Medullary Carcinoma With Lympho-Plasma Cell Infiltration:

Fifty-four per cent of all the types of medullary carcinoma encountered here are medullary carcinoma with lympho-plasma cell infiltration. Histologically, this type of tumour is characterised by

aggregates of lympho/plasma cells haphazardly disrupting the continuity of the sheet of the malignant syncytial cells. The lymphocytes and the plasma cells are in intimate relation with the tumour cells. Where the malignant cellular proliferation predominates over the host cellular reaction, columns of lympho/plasma cells may be seen in streams dividing and separating the tumour sheet into broad elongated, round, oval to polygonal clusters of syncytial malignant cells. Such tumours may present various types of jig-saw puzzle patterns histologically, as shown in figure 49. In some other types of medullary carcinomas, lympho/plasma cell infiltration may appear predominant over the malignant cellular proliferation. In such cases, the tumour mass may become over-run by lympho/plasma cells. The broad continuity of the neoplastic sheet is then broken up into columns, and into smaller clusters of malignant cells by the host cellular infiltrate. Where the lymphocytes predominates over the plasma cells, the malignant tumour cells may become dissociated into singles by the teeming lymphocytes. In such cases, an occasional isolated malignant cell may be observed with lymphocytes that have migrated into their cytoplasm (fig.50), by a process known as emperipolesis which was first described and named by Pulvertaft (1959).

In some cases lymphoid follicles with germinal centres may

be seen (fig. 51). There are some medullary carcinomas in which the infiltration by plasma cells may predominate over the lymphocytes, while in other cases, there may be balanced presence of lymphocytes and plasma cells. Such tumours may present variegated histological picture with areas of coagulative necrosis associated with plasma cells, alternating with areas where the malignant cells have undergone cytotoxic changes, and are replaced by massive lymphocytic infiltration.

Medullary Carcinoma composed mainly of Malignant Giant Cells:

In about 12 per cent of medullary carcinomas, the component malignant cells are mainly tumour giant cells. Sometimes these tumour giant cells are in combination with the typical syncytial type, but the giant cells always predominate the picture (figs. 52 and 53). The cells are large and vesicular. A tumour giant cell may contain two to four or more nuclei, with large multiple nucleoli and prominent plump chromatin granules (fig. 54). Bizarre mitosis may be abundant. This type of malignant tumour is usually prone to rapid growth. Where lymphocytic infiltration is predominant, the malignant cells are often dissociated into single cells which may be widely separated from each other by aggregates of lymphocytes. Evidence of cytotoxic changes in the malignant cells are usually observed in such tumours, where the nuclei of some malignant cells show pyknosis, and

karyorrhexis. When karyolysis has occurred in such tumour cells, they may be engulfed by histiocytes and then become replaced by lymphocytes. Medullary carcinomas composed mainly of tumour giant cells, are usually associated with areas of haemorrhage and necrosis, the latter being always accompanied by predominance of plasma cell infiltration as the main host cellular response. Vascular invasion is common with such tumours.

Medullary Carcinoma with Polymorpho-Nuclear Leucocytic Infiltration:

This is the second commonest type of medullary carcinoma seen here. It comprises 22 per cent of all the types of medullary carcinoma. Polymorpho-nuclear leucocytes are the predominant host cellular reaction to their presence. The majority of such tumours have little or no lympho/plasma cell infiltration intimately interspersed among the neoplastic cells. Under the low power microscope, such tumours are often seen with ovoid to polygonal zones of nests of malignant cells resembling areas of squamous metaplasia. Such areas are haphazardly scattered in the central areas of the syncytial neoplastic mass (fig. 55). Haagensen (1971), in his text book of Disease of the Breast, has illustrated this type of degenerative change in his figures 32 - 19, page 601, but mistakenly described it as an area of squamous metaplasia in mammary

carcinoma of the circumscribed type. There is of course, no doubt that squamous metaplasia is sometimes observed in some medullary carcinoma and even in some cases, carcinoma of the breast with squamous metaplasia has been observed in this series. But in the particular case under consideration the high power magnification of an area of this lesion appears to show ballooning, and hyaline, degeneration of the malignant cells. The nuclei are seen in various stages of degeneration pyknosis, karyorrhexis and karyolysis. The abundent cytoplasm of such cells are eosinophilic and granular (fig. 56). Where karyolysis has occurred, the ballooned malignant cells appear as ghost cells with homogeneous pink cytoplasm. Such cells, with distinct cellular borders are distorted into various shapes and forms. They become elongated, oblong, ovoid, to polygonal in shape. Host neutrophils subsequently migrate into such areas of degeneration, initially in small numbers. These inflammatory cells may be seen in the cytoplasm of the ballooned malignant cells and in between the clusters of neighbouring viable tumour cells (fig. 57). In time more polymorphs may swarm into these areas (figs. 58 and 59). Many of such invaded degenerate neoplastic cells eventually undergo liquefaction necrosis. As this happens, the areas formerly occupied by them, become replaced

by colloid-like coagulum (fig. 60). Such a eosinophilic coagulum is often irregularly lined by viable neoplastic cells. Neighbouring areas of such coagulum may sometimes coalesce to form larger cystic cavities, containing nuclear and cellular debris floating in the eosinophilic material (figs. 61 and 62). In some areas, nests of neoplastic cells, fenced by polymorphs, may be seen floating in the coagulum. An individual tumour cell may be seen with an engulfed polymorph in its cytoplasm (fig. 63). With progress of the disease, histiocytes and fibroblasts migrate from the stroma of the surrounding neoplastic mass towards the coagulum. The histiocytes phagocytose the coagulum while the fibroblasts lay down collagen which, together with the sprouting young capillaries, form a granulation tissue which in turn replaces the coagulum (fig. 64). Such a granulation tissue is initially infiltrated by polymorphs, plasma cells, lymphocytes and occasional eosinophils, but eventually it matures into a well formed fibrous tissue. Consequently, the areas formerly occupied by the ballooned degenerate neoplastic cells become replaced by fibrosis (fig. 64).

Thus, in sections from breast lesion due to medullary carcinoma with pblymorphonuclear leucocytic infiltration, the following various histological patterns in combination may be found :

(a) Initial foci where neoplastic cells have undergone

ballooning and hyaline degeneration and infiltrated by a few polymorphs. These may be seen in crops as early manifestation of this type of tumour. In time polymorphs migrate into such areas in large numbers, forming what appears like tumour abscesses of various sizes in the tumour centre. These abscesses like areas are surrounded by viable cellular tumour sheets.

(b) Foci where eosinophilic coagulum, walled off by non-degenerate malignant cells, contain nuclear and cellular debris or clusters of malignant, dying neoplastic cells surrounded by polymorphs, some of which may be found in the cytoplasm of the malignant cells.

(c) Foci of central fibrosis where young connective tissue initially abundant with polymorphs, now become moderately, and sometimes heavily infiltrated by lymphocytes, plasma cells and occasional eosinophils.

It is constantly observed that the areas of fibrosis in this type of medullary carcinoma are central and always surrounded by sheets of viable tumour cells (fig. 64). In older lesions the continuity of previously syncytial mass of this type of medullary

carcinoma, may be broken up into various mossic patterns and shapes by this centrally placed organised fibrous connective tissue. Short and moderately broad fibrous bands may be seen anastomosing with the neighbouring ones, following the pattern of the original cavity filled with the coagulum. No matter how broad or elongated the fibrous bands may be, they are always surrounded by sheets of neoplastic cells., The typical syncytial pattern of the rest of the tumour is often maintained. This is evidenced by the continuous presence of broad, elongated cellular sheets thrown into various folds that are in continuity (figs. 65 and 66). Another characteristic often observed in this type of medullary carcinoma, is that the centrally placed areas of fibrosis are characteristically separated from the main fibrous capsule of the tumour by sheets of viable neoplastic cells. This centrally placed fibrous tissue, does not cut across the breath of surrounding tumour sheet to blend with the main tumour fibrous capsule.

There are some medullary carcinomas where the host cellular reaction is a mixture of lymphocytes, plasma cells, and polymorphonuclear leucocytes. Such tumours may show different areas of cellular activity according to the predominance of the type of the host cellular reaction. In areas where lymphocytes predominate,

most of the tumour cells may have undergone cytotoxic changes and become replaced by aggregates of lymphocytes. Such areas, may be seen alternating with areas of coagulative necrosis associated with abundant plasma cell infiltration or with cystic areas containing eosinophilic coagulum and surrounded by viable tumour cells which are infiltrated by polymorpho-nuclear leucocytes (fig. 67). Eosinophilic cellular infiltration, which may be scanty or massive, is always found in medullary carcinomas with polymorho-nuclear leucocytic infiltration. They are always commonly found at the periphery of the tumour mass and occasionally in the centrally placed connective tissue which is surrounded by viable tumour cells.

Medullary Carcinoma with neither Lympho-Plasma Cells nor Polymorpho-Nuclear Leucocytic Cellular Infiltration:

This is a type of medullary carcinoma in which the rate of mitosis and malignant cellular proliferation are so rapid that it seems the host is incapable of producing immune cellular response to it. It is encountered in 12 per cent of all the types of medullary carcinoma occurring locally. Histologically, the ovoid to polygonal syncytial cells that compose the tumour mass show plump chromatin granules and prominent nucleoli. The nuclei are vesicular, and mitosis are often abundant. Bizarre malignant giant cells are

commonly found in this type of tumour. As a result of their rapid rate of growth these tumours are often associated with massive central areas of necrosis (Figs. 68 and 69). The most important characteristic feature of this type of tumour is the ominious absence of either lympho-plasma cell or polymorpho-nuclear leucocytic cellular infiltration in the central areas of the tumour. (fig. 68). The stroma is scanty but in most cases it is well vascularised. Lymphatic and venous tumour emboli are common and there is always associated regional lymph node metastasis that may histologically undergo necrosis as in the primary mammary lesion.

SUMMARY:

On the whole, all these histological types of medullary carcinoma have the following characteristics in common:

1. The are all well circumscribed and encapsulated carcinomas without structures or glandular formation.
2. They all tend to grow very large and undergo coagulative, haemorrhagic or liquefaction necrosis, which in some cases may undergo dystrophic calcification.
3. The malignant cells are of epithelial origin and have a tendency to be very large with vesicular nuclei and vacuolated cyto-plasm.

4. Mitoses are usually abundant and tumour giant cells containing from 2 to 5 nuclei may be found in all the histological types.

5. Areas of haemorrhage may occur in any of the histological types, particularly in medullary carcinoma composed mainly of malignant giant cells.

The impression gained is that the lympho-plasma cell infiltration that are diagnostic of most medullary carcinoma is immune response of the host to the presence of the tumour. The lymphocytes with their cell bound antibodies, are immunologically competent cells, which by process of emperipolesis enter tumour cells, exert in them cytotoxic changes which eventually destroy them. The plasma cells, on the other hand, produce humoral antibodies that react with the tumour cells or their products as antigens, producing coagulative necrosis. It is currently thought that in medullary carcinomas with polymorpho-nuclear leucocytic cellular infiltration, the polymorphs offer another type of host cellular defence mechanism against the presence of tumour. This is a sort of inflammatory host cellular defence mechanisms effected by polymorphs. It is not an immunological response, but it appears definitely as a defence mechanism by the host against the presence of the tumour. Although it is necessary that in some cases, secondary infection to the tumour elicited by tumour cell necrosis is

to be excluded by bacteriological culture to demonstrate or exclude any pyogenic organisms, it must be borne in mind that the type of necrosis encountered here in the presence of polymorphs is liquefaction (colliquative necrosis) and not coagulative type of necrosis resulting in creamy abscess formation.

Hurley (1972) has shown that polymorphs are amoeboid and phagocytic and that in acute inflammation many polymorphs die and disintegrate in extravascular tissues and release enzymes and other active materials into surrounding tissue. Janoff (1970) has earlier shown that apart from degradative enzymes found in the lysosomes, fibronolysins and other enzymes are released by the disintegrated polymorphs. It is therefore, being hypothesised that, in medullary carcinoma with polymorpho-nuclear leucocytic infiltration, with areas of ballooning and hyaline degeneration, the polymorphs wander into the cytoplasm of the malignant cells by amoeboid motion, disintegrate and liberate their lysosome enzymes which cause liquefaction of the tumour cells. This autolytic action of lysosome enzymes on the tumour cells is responsible for the sterile liquefaction necrosis observed in this type of medullary carcinoma.

In medullary carcinoma with neither lympho-plasma cell nor polymorhpo-nuclear leucocytic cellular response, the impression

gained is that patients with such tumours may either have immunological deficiency or that their immune response by their reticulo-endothelial system may be suppressed by the tumour cells or their products. It is observed that in such tumours their necrotic areas hardly ever elicite either polymorpho-nuclear leucocytic nor lympho-plasma cell response.

TABLE XXXII

Percentage Age-Group Distribution of Histological Types of Medullary Carcinoma

Histological Types	Age-Group (Years)						
	16-20	21-30	31-40	41-50	51-60	61-70	70-80
Medullary ca. with lympho-plasma cell	-	13%	26%	43%	13%	4%	-
Medullary ca. with giant cells	-	14%	43%	29%	7%	4%	-
Medullary ca. with polymorphs	3%	13%	36%	27%	13%	7%	-
Medullary ca. with no lympho-plasma cells	-	11%	16%	42%	16%	5%	11%

Table XXXII at page 108, shows that the percentage incidence of each type of medullary carinoma increases with rising age. Medullary carcinoma with polymorpho-nuclear leucocytic infiltration is the only type found in the 16-20 year age-group women. The percentage incidence of all types is increased in 21-30 year age-group where medullary carcinoma composed mainly of giant cells appears to have the highest percentage incidence and medullary carcinoma with no lympho/plasma cell has the least. In the age-group 31-40 years, medullary carcinoma composed mainly of giant cells has still the highest percentage incidence. This is followed by medullary carcinoma with polymorhpo-nuclear leucocytic infiltration and then by medullary carcinoma with lympho/plasma cell infiltration, the least common in this age-group being medullary carcinoma with no lympho/plasma cell infiltration. In the age-group 41-50, medullary carcinoma with lympho/plasma cell infiltration has the highest percentage incidence. This is followed by medullary carcinoma with no lympho/plasma cell infiltration. In the age-group 51-60, medullary carcinoma with no lympho/plasma cell infiltration has the highest percentage incidence. This is followed by medullary carcinoma with polymorpho-nuclear leucocytic infiltration and medullary carcinoma with lympho/plasma cell infiltration. In the age-group 61-70, medullary carcinoma with

polymorpho-nuclear leucocytic infiltrate has the highest percentage incidence, followed by medullary carcinoma with no lympho/plasma cell infiltration. The only histological type of medullary carcinoma diagnosed in the age-group of 71-80 is medullary carcinoma with no lympho-plasma cell infiltration.

Medullary carcinoma with polymorpho-nuclear leucocytic infiltration occurs in nearly all age groups except in women 70-80 years of age. Its peak percentage incidence is in young women in the age-group of 31-40 years. Medullary carcinoma composed mainly of giant cells has also its peak in this age-group. Medullary carcinoma with lympho-plasma cells and medullary carcinoma with no lympho/plasma cells, both have the peak percentage incidence in much older women in the age-group, 41-50 years than the rest. The percentage of each type of medullary carcinoma increases with rising in age of women, 16-20 years, to reach its maximum in women 41-50 years old, and falls there after.

Medullary carcinoma composed mainly of giant cells and medullary carcinoma with polymorpho-nuclear leucocytic infiltration are commoner in premenopausal women (16-40 year age-group) than the remaining histological types. In the menopausal women (41-50 year age-group), the commonest histological types of medullary

carcinoma are medullary carcinoma with lympho-plasma cell infiltration and medullary carcinoma with no lympho-plasma cell infiltration, while in the post-menopausal females (51-80 year age-group), medullary carcinoma with no lympho-plasma cell may quite commonly be encuuntered. The distribution of various histological types of medullary carcinoma is therefore related to age.

C - CIRCUMSCRIBED CARCINOMA (GROUP I, B.4)

Circumscribed carcinoma accounts for 12 per cent of all the malignant mammary neoplasias here. It is the fourth commonest histological type of breast carcinoma in Nigeria. It affects both female and male breasts. It begins to afflict the breasts of females at their third decade of life. The youngest women with circumscribed carcinoma is 30 years of age, and the oldest is 71 years. Only one case is discovered in a male aged 48 years. 22 per cent of all circumscribed carcinoma are discovered in women 30 to 39 years of age. 42 per cent in women 40-49 years of age and 37 per cent in women 50-89 years of age. It is therefore mainly a carcinoma of the menopausal and post-menopausal women. The average age of women with circumscribed carcinoma is 44.3 years, their median age, 43.8 years, and their modal age, 43 years.

Histologically, circumscribed carcinomas are characterised by their rounded borders and by their fibrous capsule which are usually heavily infiltrated by lympho-plasma cells and occasional eosinophils which are always present at the periphery of the tumour as illustrated in figs. 70 and 71. These tumours are always of multicentric origin. They are always mutilobular in

pattern. Fibrous septa are always seen ramifying from the fibrous capsule towards the tumour centre. They divide into smaller septa, enclosing each tumour lobule. The fibrous septa may be sparsely infiltrated by lympho-plasma cells as seen in figure 49 or massively as shown in figure 72. It is the characteristic of these type of tumours that the lymphocytes and the plasma cells always aggregate at the periphery of the tumour lobules. They are not seen infiltrating into the tumour mass to be intimately interspersed among the malignant cells as occurs in medullary carcinoma. This is a significant morphological difference between syncytial medullary carcinoma and circumscribed carcinoma which is well appreciated when one compares the medullary carcinoma with lympho/plasma cell infiltrate in figure 73, with the circumscribed carcinoma in figures 70, 71 and 72. In the former, sheets of malignant vascular syncytial cells are seen enclosing lympho-plasma cell aggregates which are in intimate relationship with the tumour cells centrally, while in figure 50, circumscribed carcinoma, aggregates of lympho-plasma cells gather at the periphery of the tumour lobules. Central fibrosis can be massive in circumscribed carcinoma. In this type of tumour, it is constantly observed that the fibrous tissue at the tumour centres always invariably surround the tumour cellular masses which form small or larger nodules as has been

illustrated in figure 74. Here the fibrous tissues infiltrated by lympho-plasma cells are seen to be traceable to the capsule of the tumour as illustrated in figure 75. In contrast, central areas of fibrosis infiltrated by lympho-plasma cells, when observed in some medullary carcinomas, is scanty, and always surrounded by sheets of anastomosing malignant cells which are in continuity as shown in figures 64, 65 and 66.

Thus the mossic pattern observed in circumscribed carcinoma is due to anastomosing strands of fibrous trabeculae that ramify centrally from the tumour capsule, surrounding nests of tumour cells while that observed in some syncytial medullary carcinoma is due to anastomosing bands of syncytial maligant cells centrally enclosing fibrous connective tissue that are infiltrated by lympho-plasma cells. Another characteristic peculiar to circumscribed carcinoma is that the component malignant epithelial cells of each nodule may be structured to form glandular patterns, papillary or tubular structures characteristics of some histological types of breast carcinoma. Histological patterns seen in circumscribed carcinoma of a breast lesion may vary from lobule to lobule. Thus in a breast lesion of this type, one lobule may show glandular pattern while another may have medullary pattern that may undergo central necrosis. Various

patterns may be found in a tumour lobule, thus elongated coreless papilae, sometimes with tubular formation, may be seen in combination with nests of tumour cells, as illustrated in figures 76 and 77. In some cases, the malignant epithelial component cells of circumscribed carcinoma are mainly composed of giant cells.

Eighteen per cent of axillary lymph nodes in females with circumscribed carcinoma are malignant. Depigmentation of the overlying skin is often associated with very large circumscribed carcinoma. 19 per cent of this tumour is associated with fibrocystic disease of the breast.

D - PAGET'S DISEASE OF NIPPLE (GROUP I, C.4)

Paget's disease of nipple is the 8th commonest histological type of female breast carcinoma. It accounts for 4 per cent of all the mammary malignancies in the female. Only one case of this type of carcinoma is diagnosed in a 70-year old male. The youngest female with Paget's disease of nipple is 31 years old and the oldest, 64 years of age. The mean age of the females is 44 years, the median age, 40.5 years and the modal age, 40 years. Twenty-sevnn (27) per cent of Paget's disease occurs in 30-39 year age-group, 47 per cent, in the 40-49 year age-group, 20 per cent in the 50-59 year age-group, and 7 per cent in the 60-69 year age-group women. Paget's disease of the nipple is therefore mainly a disease of menopausal and postmenopausal women in this society.

Paget's cells are large malignant cells with pale finely granular cytoplasm and prominent hyperchromatic nuclei which, in early cases of Paget's disease of the nipple, are seen scattered singly in the basal layer of the nipple epidermis (fig. 92), and sometimes among the epithelial cellular lining of lactiferous ducts and hair follicles (fig. 93). In some cases Paget's cells form nests or clumps that are seen scattered in

the nipple epidermis (fig. 94). In most cases of early Paget's disease, the nipple epidermis is often hyperkeratotic and acanthotic with some degree of depigmentation. In advanced cases, Paget's cells are increased in number, compressing the epidermal squamous cells to such an extent that the squamous cells are thrown into various alongated shapes, forming a net-work, the meshes of which are filled with Paget's cells lying single or in groups (fig. 95). In most cases of Paget's diseases seen in Nigeria, Paget's cells have a tendency to accummulate melanin granules in their cytoplasms. The melanin may be limited in amount, but occasionally the Paget's cells may contain so much melanin that the epidermal lesion may closely resemble an intraepidermal malignant melanoma from which it must be differentiated (fig. 96). The presence of Paget's cells in the nipple epidermis is almost invariably associated with moderate to massive host cellular reaction consisting mainly of lymphocytes, plasma cells, histiocytes and occasional eosinophils (fig. 97). These cells usually form a cellular band just below the basement membrane of the diseased nipple epidermis. The histiocytes are often laden with melanin pigments in black skins. The smooth muscles in and around the nipple in Paget's disease are often remarkably hypertrophied and prominent (fig. 98), thus explaining the nipple erection so often observed in face of advanced Paget's disease.

All the Paget's diseases of nipple reviewed in these series are associated with an underlying intra-mammary carcinoma. Thirty-six per cent of the cases are associated with underlying intraductal carcinoma (fig. 99) which shows solid intraductal and comedo-carcinoma in combination. This histological type of carcinoma is associated with the Paget's cells shown in figure 92. In some cases the intraductal carcinoma may present stromal invasion by carcinoma with diffuse fibrosis (figs. 100 and 101). The underlying intra-mammary carcinoma in twenty-one per cent of the cases is typical medullary carcinoma with lympho-plasma cell infiltration (fig. 101), which is associated with the Paget's cells shown in figure 93. A case of invasive lobular carcinoma, nodular in pattern and composed mainly of nests of Pagetoid cells (fig. 103) is seen associated with intra-epidermal Pagetoid cells in figure 94. Other types of underlying intra-mammary carcinoma associated with Paget's disease of nipple, observed in the series are :

(a) carcinoma with diffuse fibrosis (29 per cent);

(b) circumscribed carcinoma (7 per cent); and

(c) papillary carcinoma (7 per cent).

E - INVASIVE PAPILLARY CARCINOMA (GROUP I, B.5)

This is the commonest histological type of breast carcinoma in Nigerian males. It accounts for 38 per cent of all mammary malignant lesions in the males, and 9 per cent in the females. Papillary carcinoma begins to afflict the female breasts at much younger age than males. The youngest female patient with this histological type of carcinoma is 20 years of age, while the youngest male is 31 years of age. The average age of females with papillary carcinoma is 42.1 years, their median age, 42.3 years, and their modal age, 42.3 years, while the average age of the male counterpart is 49.7 years, the median age, 52 years and the modal age, 55 years.

TABLE XXXIII

DISTRIBUTION OF

Female/male Papillary Carcinoma to Various Age-Groups

Papillary carcinoma	Age-Group						
	20-29	30-39	40-49	50-59	60-69	70-79	80-89
Female	3%	22%	47%	16%	16%	-	-
Male	-	13%	13%	63%	13%	-	-

Table XXXIII at page 119, compares the percentage distribution of female papillary carcinoma to various age-groups with that of the male. Papillary carcinoma occurs in the females at much earlier age-group than the males. Its peak incidence is observed in 40-49 year age-group in females and in 50-59 year age-group in males.

Microscopic Features:

There is no observed difference betwen the histological types of papillary carcinoma seen in both male and female lesions. There is also no difference between the intracystic papillary carcinomas, and invasive papillary carcinoma seen locally for most papillary carcinomas are intracystic and may have already spread to the neighbouring breast tissue, with lymph node metastases before most patients present themselves to the surgeons. Papillary carcinoma may be of multicentric origin. Commonly they are associated with multiple, cystically dilared ducts, some of which are lined by malignant epithelial cells which are either single or multilayered (fig. 78). The cells lining the cysts are flattened in single layers in places, and heaped up as cuboidal or low-columnnar epithelial cells in others, (Fig. 79). With progress of the lesion, malignant syncytial cellular masses are seen in focal areas projecting towards the

centre of the cystic cavities (fig. 80). From such cellular projections are formed either the short or elongated coreless papillae in which malignant cells form almost syncytial masses with indistinct cellular borders, and without any central connective tissue core usually found in papillary lesions. Several cystic cavities in different sectors of a lesion, may be involved in this type of malignant change. Some larger cysts, filled with eosinophilic proteinaceous secretion of the malignant cells, may contain clusters of malignant cellular dropouts, surrounded by clear spaces, and scattered here and there in the coagulum (fig. 81). In some areas of the same tumour, the projecting elongated syncytial masses may anastomose with each other, enclosing spaces of various sizes and shapes to form the cartwheel pattern of papillary carcinoma (fig. 82). Invariably, the neighbouring mammary tissue, and the regional lymph nodes, are often invaded by cluster of malignant syncytial cells, each cluster being always surrounded by a clear space. Where many tumour clusters have invaded mammary parenchyma, they may appear to aggregate in spaces, with scanty fibrous connective tissue stroma interventing, (figs. 63, 80 and 83).

The other type of papillary carcinoma encountered locally, is one in which the mammary ducts are cystically dilated by malignant papillae with central fibro-vascular connective tissue cores. Such

papilae may occupy the whole cystic cavity. Dropouts of clusters of smaller papillae due to tangential section cutting of papillae may be seen floating in the centres of coagulum secreted by the cells of such malignant papillae (fig. 84). It is often such small papillae with central connective cores that invade the surrounding breast tissues and metastasize to the regional lymph nodes.

Papillary carcinoma with cribriform pattern (figs. 85 and 86) and cart-wheel pattern, either alone or in combination are often seen in association with either the carcinoma with coreless papillae as shown in fig. 87, or with carcinoma with central fibro-vascular connective tissue cores. In some papillary carcinomas, an area of cribriform pattern may be seen almost in continuity with solid papillarycarcinoma as shown in fig. 88. The most invasive forms of papillary carcinoma encountered here, are the ones consisting of short and elongated coreless papillae. They commonly invade the breast tissue diffusely. Fig. 89 is a photomicrograph of such a tumour from a male breast lesion. The centrally placed duct is moderately dilated, and shows moderate periductal fibrosis. Elongated and short coreless malignant papillae, surrounded by clear spaces, are spread diffusely in the surrounding mammary tissue. The tumour stroma is scanty and is sparsely infiltrated by lympho-

plasma cells. Figure 90, is the high power view of fig. 89, showing the syncytial malignant cells with pleomorphic vesicular nuclei and prominent nucleoli. Figure 91, shows the lymph node metastasis of this type of tumour.

In general, most invasive papillary carcinomas encountered in both Nigerian females and males are those with coreless papillae, those with central vascular connective tissue cores, and those portraying cribriform and cartwheel patterns. All these may be found in combination in one breast lesion, which is usually multilobular. The fibrous stroma of such tumours may be either scanty or abundant, particularly with invasive tumours that exhibit cartwheel pattern. Male papillary carcinomas often show marked stromal desmoplasia than the female tumours. The host cellular reactions to the presence of papillary carcinomas are usually lymphocytes, plasma cells and eosinophils, which may be scanty or abundant. Eosinophils are commonly present at the peripheral borders of most papillary carcinomas. Necrosis in majority of cases may be massive and are often associated with microcalculi. Massive invasive papillary carcinoma are often associated with depigmentation of the overlying epidermis. 22 per cent of invasive papillary carcinoma is associated with fibrocystic disease of the breast.

F - MALIGNANT BREAST NEOPLASIA IN PREGNANCY AND LACTATION IN NIGERIA

Because of the obstetrical and gynaecological importance of neoplasms of reticulo-endothelial origin in Nigeria, this study is concerned with brief clinical abstracts of two histological types of this group of malignant mammary disease seen here.

Clinician in charge of the 2 cases - Mr. J. I. Durodola, Surgery Department, University College Hospital, Ibadan (1976).

CASE NO. 1

History:

A 35-year old woman (her last confinement was 5 years and her last menstrual period was 1 year before, but she was breast feeding her grand-child,(a practice that is quite common in this part of Nigeria) was admitted to the hospital with 2 months history of swelling of left breast with severe itching. She was para 4, gravida 4, 2 children alive. She breast fed all her children.

Clinical Findings:

(1) Breast lesion - Clinical examination revealed huge left breast, nodular in parts, hard cord like masses palpable; skin area over parts of the breast was inflamed and partly covered with dry scabs (photograph 11).

(2) On admission -

(a) Her temperature was 100.2°F orally

(b) Haematocrit - 32 per cent

(c) W.B.C. - 4800/mm^3

Treatment:

(1) Simple mastectomy

(2) Cyclophosphamide

(3) Good response - discharged after one month hospitalisation.

(4) Five months later, nodular swelling appeared around the mastectomy scar, with itching.

(5) Another course of cyclophosmaide.

She died 12 months from the time she was first seen.

CASE NO. 2

History:

A 21-year old lactating woman (last confinement 2 months previously) was admitted to University Teaching Hospital, Ibadan with 1 month history of painful swelling of right breast which was increasing rapidly, weight loss, 1 week history of fever, shortness of breath and productive cough. A few days before admission she felt much worse with biting pain in her

right breast, orthopnea, bleeding from the breast growth. She had no previous illness and no allergies or trauma. She was a para 3, gravida 3, one child alive; she breast fed all her children.

Clinical Findings:

(1) Breast Lesion - Clinical examination shows a large hard warm right breast fixed to the chest wall, indurated, showing peau d'orange with 4 infected incisional wounds made the day before admission in an attempt to drain a misdiagnosed breast abscess (photographs 12 and 13). Left breast had 3 hard lumps attached to the skin but not to deep structures (photograph 12).

(2) On admission -

(a) Her temperature was 100.6°F (orally)

(b) Haematocrit - 12 per cent (normal 36-37 per cent)

(c) W.B.C. - 60200/mm^3 with a shift to the left.

She had staphylococcal septicaemia from secondary infection of the incised breast tumour.

Treatment:

(1) Blood transfusion

(2) Antibiotics

(3) Methotrexate and Methyl testosterone

(4) Cyclophosphamide

(5) Bilateral oophorectomy.

She died 66 days after admission. Autopsy was refused.

PATHOLOGY OF THE TWO CASES

Case No. 1

Gross Appearance - Received mastectomy specimen weighing 1957 gms. The breast is enlarged with lobulated ill-defined tumour mass with surface ulceration. The nipple is not retracted but there are patchy areas of hypopigmentation in the skin overlying the tumour. The cut surface of the tumour is lobulated, and has fish-flesh appearance. There is infiltration of the skin and the underlying skeletal muscles.

Microscopy:

The sections show Burkitt's lymphoma consisting of diffuse proliferation of undifferentiated lymphoid cells and scattered macrophages that contain nuclear and cellular fragements giving the starry sky appearance as shown in figs. 104 and 105. The tumour

sheet is well circumscribed and sharply demarcated from the surrounding breast tissue, but not encapsulated. The proliferating lymphoid cells diffusely infiltrate the mammary tissue almost completely replacing its parenchyma, with invasion of the underlying skeletal muscle (fig. 106). Characteristically, the proliferating lymphoid cells are seen invading the tunica adventitia of the blood vessels, and the perineurum of the nerve bundles without invading the vessles, or the nerve bundles as shown in figs. 104 and 107. Higher magnification of the tumour shows the predominance of undifferentiated lymphoid cells with the nuclei showing delicate chromatin granules and relatively small nucleoli. The pale large histiocytes have vesicular nuclei, some containing cellular or nuclear debris which they have phagocytosed (fig. 105). Imprints taken from biopsy of such Burkitt's lymphoma tissue and stained with May-Grunwald stain or any of the Romanowsky stains show lymphoid cells with intense cytoplasmic basophilia, and the presence of variable numbers of vacuoles from which neutral fat has been dissolved during fixation as shown in fig. 108. These are striking features of Burkitt's lymphoma cells observed readily at the edges of the imprints where lymphoid cells have separated from each other. Study using the oil immersion objective may benecessary to detect the neutral fat vacuoles

Case No. 2

The histology of this case type is first illustrated with sections obtained from a mastectomy specimen from a 26-year old lactating female with primary reticulum cell sarcoma of the breast.

Microscopy:

The sections show reticulum cell sarcoma (large cell lymphoma) consisting of diffuse proliferation of neoplastic cells, interspersed among them are numerous phagocytosing cells, replacing completely the breast tissue (fig. 109). On high magnification the neoplastic proliferating histiocytes show distinct and relatively thick nuclear membranes, irregular nuclear chromatin distribution and large irregular nucleoli, with abundant cytoplasm (fig. 110). Mitosis may or may not be abundant. The malignant histiocytes may have engulfed nuclear or cellular debris in their cytoplasm. Sometimes large atypical multinucleated giant reticulum cells are found interspersed among the profiliferating lymphoid cells (figs. 110 and 111). Areas of liquefaction necrosis may be present as shown in fig. 113. Eosinophils are present here and there. The reticulum stain may show reticulin fibres encircling individual malignant cells, but in the case under consideration, the reticulin fibres appear condensed in some places; these probably representing the pre-existing fibres of the stroma as shown in fig. 114. Figures 115 and 116

show a photomicrograph taken from a section obtained from the oophorectomy specimen of the Case No. 2, photograph 12. The proliferating malignant cells, many with bean shaped nuclei, have completely replaced the ovarian tissue. Abundant eosinophils are interspersed among the malignant cells. Mitosis are plentiful.

Primary Burkitt's lymphoma, and reticulum cell sarcoma, of the breast are both neoplasms of reticulo endothelial origin. Burkitt's lymphoma begins to afflict the female breast from menarche. The youngest female with primary mammary Burkitt's lymphoma in the series is 12 years of age. There are twelve cases of primary Burkitt's lymphoma observed in the female breasts, with age range from 12 to 35 years. Only two cases are discovered in two young males aged 13 years and 15 years respectively. Reticulum cell sarcoma on the other hand occurs in both female and male. It begins to afflict the breast of women at much older age than Burkitt's lymphoma. The youngest female with this disease is aged 21 years, the age range of such afflicted women being between 21 and 35 years. The only male case in the series is found in a 45-year old man.

The importance of these two histological types of malignant lymphoma, lies in the fact that both afflict the breast of young women in their early reproductive life, particularly during pregnancy and lactation. The similarity between the age distribution pattern of patients with Burkitt's lymphoma and reticulum cell sarcoma in women of this particular group is shown in Table XXXIV and the total number of the case types along with their average ages, with their standard errors are shown in Table XXXV.

TABLE XXXIV

Actual Age-distribution of the Two-Case Types

Age (in years)	Burkitt's lymphoma	Reticulum cell sarcoma
12	1	-
13	2	-
14	3	-
19	1	1
20	1	-
21	1	2
25	1	3
26	1	-
28	-	1
29	-	1
35	1	1
TOTAL :	12	9

To find out whether the age range of the two groups is statistically significant, the hypothesis to be adopted is that there is no

significant difference between the age distributions of the two case types. The alternative hypothesis is that cases of reticulum cell sarcoma occur at a higher age on the average than cases of Burkitt's lymphoma. In order that this hypothesis may be tested the "t" statistic is applied. The necessary calculations has given a "t" value of 2.36. The tabulated value of "t" distribution with 19 degrees of freedom (one tail) 2.5 per cent point is 2.10, and 1 per cent point is 2.54. Therefore there is a significant difference between the age distributions of the case types.

TABLE XXXV

Number of Case-types, Averate age with their Standard Error

	Burkitt's lymphoma	Reticulum cell sarcoma
No. of Cases	12	9
Average Age	18.3	25.3
Standard Error of average age	2.03	1.63

This is to say that the alternative hypothesis, that cases of reticulum cell sarcoma occur at a higher age, on the average, than cases of Burkitt's lymphoma, holds. Burkitt's lymphoma and reticulum cell sarcoma of breast, both have similar clinical

presentations. The primary signs and symptoms being located in the breasts. Both types of lesion appear suddenly in pregnant or lactating women, involving one or both breasts at the same time. The breast tumours in both cases are diffuse, rapidly growing lesions, accompanied by signs of acute infilammation that mimick breast abscesses, which is not uncommon in lactating breasts. In fact, both present as inflammatory carcinoma (mastitis carcinomatosa) as illustrated from the case histories above. The histology of the two case types are distinct, as has been illustrated. The clinical approach is the same, as both conditions may be treated by mastectomy followed by cytotoxic drug therapy. But usually, in some cases, the patients may be so moribund with wide spread metastases that cytotoxic drugs may be the only therapy of choice. The prognosis is very bad in both cases, the afflicted individuals dying within a very short time soon after the presentation of the case. Since it has been clinically shown that Burkitt's lymphoma usually responds to chemotherapy, it is important to differentiate it from other types of neoplasm that may occur in women between 19-35 year age-range which in some cases, may present as acute inflammatory carcinoma. These are mainly typical syncytial medullary carcinoma, carcinoma with diffuse fibrosis (scirrhous carcinoma), circumstribed carcinoma, intraductal carcinoma, invasive lobular carcinoma, and invasive

papillary carcinoma. The final diagnosis in most cases is made with haematoxylin-eosin stained routin sections, but the diagnosis of Burkitt's lymphoma, can be rapidly made with imprints stained with any of the Romanowsky stains as has already been stated.

PART THREE

E V A L U A T I O N

CHAPTER IV

(a) D I S C U S S I O N

Review in Literature:

The ancient nation that cancer was rare or absent in the tropics, Renner (1910), Hoffman (1915), Blair (1923) is no longer acceptable in the modern time. This statement is further strengthened by the fact that a great deal of information has been given on cancer incidence rate in various parts of Africa by various other European authors: Nigeria, Edington and Maclean (1965); Uganda, Davies, Kwowelden and Wilson (1965); Portguese East Africa, Prates and Torres (1965); and South Africa, Higgins and Oettle (1960). Doll, Muir and Waterhouse in their book on'cancer incidence in five continents' have recently made available the findings of these surveys in tropical areas and comparable findings from temperate zones are also included. It is felt that in most areas of the tropics the incidence of cancer is less than half of that recorded in temperate zones and that cancer patterns differ markedly between tropical and temperate zones of the world.

Analysis of Cancer Registry Records:

The Cancer Registry here recorded up to twelve-thousand, four-hundred and fifty-five (12,455) cases of cancer of all sexes from various organs of the body during the 16-year period of this study.

A higher proportion of the cases are found in females. The relative ratio frequency of carcinomas is 54 per cent as against 24 per cent of sarcomas. Locally therefore, carcinomas are commoner than sarcomas, a conclusion similar to that arrived at long ago by Smith and Elmes (1934) in Nigeria. Vint (1935) simultaneously, as the latter Nigerian authors, came to the same conclusion in Kenya. The earlier statement made by Blair (1923) that he never saw a case of either cancer or sarcoma in Nigeria appears therefore, incorrect. Also, Macfie's (1923) conclusion that sarcomas were more frequent than carcinomas in Africa is at variance with the current findings.

It is true that malignant diseases are as common in Africa as elsewhere in the world, Alder and Cummings (1923). It is also true that malignant diseases are not infectious and as such are not transmissible from one person to another. Renner's (1910) statement that earlier European workers in Africa had infected the African indigens who came in contact with them with cancer is therefore not acceptable. It is, however, agreed with Alder and Cummings (1923) that European civilization was wrongly blamed for spread of cancer in Africa, when it had only been responsible for its diagnosis.

General Pattern of Breast Diseases:

Mammary lesions in Nigeria are usually due to (1) infective causes, (2) non-infective benign lesions, such as fat necrosis, fibrocystic disease of breast, mammary duct-ectasia and gynaecomastia, and (3) mammary tumours, which may either be benign or malignant. Most infective breast lesions here occur in all ages but they are particularly prevalent in neonates, infants and in women during puerperium and lactation. Their recorded rate here is low simply because the canger registry records mainly tumours. Infective lesions in the registry are therefore, cases recorded by chance. They are generally cases clinically misdiagnosed as cancer when the biopsies were taken. The most common here are unresolved pyogenic mammary abscesses. It is important to point out here that granulomatous lesions such as tuberculosis, schistosomiasis and onchocerciasis do cause hard breast lumps that mimick breast cancer in most parts of the tropics. Fat necrosis, which appears to be solely the disease of female breast, do also mimick breast cancer in its clinical presentation. Diagnostic biopsy of all breast lumps before surgery is therefore, mandatory in order to exclude these uncommon benign breast lesions in the tropics.

Fibrocystic disease and mammary duct ectasia in the female, and gynaecomastia in the male, are the most important non-infective benign lesions of the breast encountered here. The former two lesions, (the mammary dysplasias) are respectively the third commonest causes of breast disease locally. They occur in much older patients than most benign mammary lesions with peak age incidence in the third and fouth decade of life, respectively. In Nigeria, gynaecomastia is second to carcinoma as one of the commonest causes of male breast lesions. Fibroadenoma and giant fibroadenoma are both benign tumours of breast. The former is mainly diagnosed in females. It is the commonest cause of breast tumour in Nigerian young females. The latter, giant fibroadenoma, is not as common as fibroadenoma, and it afflicts both female and male breasts. Malignant breast lesions are definitely the commonest causes of breast diseases in both Nigerian females and males. Although they are generally the diseases of older patients, sarcomas, particularly primary Burkitt's lymphoma of breast, are usually the malignant diseases of young female and male patients.

It is observed that some of the breast diseases found in Nigeria are equally commonly found in other parts of the world. From West Indies (Jamaica), Harris (1977) presented the percentage

distribution of various breast lesions diagnosed in Jamaican women and compared his result with the figuresSymmers (1966) and Templeton (1973) presented for the English and Uganda females respectively, as follows, in Table XXXV.

TABLE XXXV

PERCENTAGE DISTRIBUTION PATTERN OF VARIOUS BREAST LESIONS IN JAMAICA, ENGLAND AND UGANDA (HARRIS, 1977)

Breast lesion	Jamaica (%)	England (%)	Uganda (%)
Carcinoma	37.2	41.0	62.5
Fibroadenoma	32.4	11.4	11.1
Cystic disease including ectasis	26.5	42.8	8.2

It is obvious from the figures of Harris that the commonest cause of breast disease in Africa (Uganda) is carcinoma, in Great Britain (England), cystic disease including mammary duct-ectasia, while in West Indies (Jamaica) it is fibroadenoma. All these breast diseases have been shown currently to occur in Nigeria where the commonest cause of breast disease is carcinoma followed by fibroadenoma and by fibrocystic disease including mammary duct-ectasia. The African countries, (Nigeria and Uganda) would appear to have similar

distribution pattern of breast lesions that is different from that of Great Britain, where the commonest cause is fibrocystic disease including duct-ectasia followed by carcinoma and then by fibroadenoma. The African, and the British, distribution pattern, respectively, appear different from that of West Indies where the commonest cause is a benign tumour, fibroadenoma, followed closely by carcinoma and fibrocystic disease including duct ectasia. Also according to Harris (1977), breast lesions afflict the left more than the right breast in American and West Indian women, while in Nigeria the right is afflicted more than the left breast.

In summary, breast lesions do occur all over the world but there would seem to be obvious geographical differences in their patterns of distribution in Africa, Great Britain, West Indies and perhaps, throughout the world.

Specific Study on Breast Cancer:

Out of a total of 725 of breast cancer recorded in the Cancer Registry during the 16-year period of this study, 97 per cent are female, and 3 per cent are male cases, respectively. The frequency of breast cancer is about 38 cases per annum. There is an observed increase in the year 1969-75 compared with 1960-69. This slight increase may perhaps, be due to higher diagnostic yields during those

periods, as more surgeons and pathologists began focusing more attention on the problems of breast cancer in Nigeria.

There is neither mortality nor prevalence data on breast cancer in the registry and as such, the actual total number of cases of breast cancer in Ibadan community at any given time is not known. However, breast cancer with a relative ratio frequency of 6 per cent, and 5.8 average annual incidence per 100,000 (all ages) in estimated Ibadan female population of 269,000 is second to carcinoma of cervix as one of the major clinical problems in Nigerian women. Breast cancer is a disease much less frequent in Nigeria than in most European and American countries. Robbins (1957) observed that breast cancer is equally a major clinical problem in American women, and is responsible for about 20,000 to 25,000 deaths of American women per year. Haagensen (1971) recently declared mammary cancer as one of the great diseases in America where in 1966 there were about 27,304 deaths from it alone. Segi, and Kurihara (1966) published the data on the mortality rate of breast cancer, for the years 1964-65 in 24 selected countries (mostly Europe and America), and computed the death rates by age adjusted to a Japanese standard population. Their study emphasized the striking variations in the toll of breast cancer in different countries of the world. They found the highest

mortality rate in Netherlands, England and Wales, Scotland and America and a lower rate in France, Italy and Japan. They showed that breast cancer is very much less frequent in Japan than in most European and American countries. Doll, Muir and Waterhouse (1970) quoted the average annual incidence of breast carcinoma per 100,000 of Japanese female population as 10.5 as against Nigerian female figure of 5.8. It follows that the frequency of breast cancer in Nigerian female population is about half of that of Japanese female population and about ten times less than those obtained in most European and American women. In order to verify whether there is real geographical differences in breast cancer incidence between African countries and European and American countries, figures of breast cancer per 100,000 of age-adjusted standard population of various countries compiled in "Cancer Incidence in Five Continents" by Doll, ,Muir and Waterhouse (1970) for some selected races of the world are compared in (a) table XXXVI, for coloured female races; (b) table XXXVII, for white female races; (c) table XXXVIII, for coloured male races and (d) table XXXIX, for white male races.

TABLE XXXVI

Female Coloured Races: Breast Cancer Incidence Rate, per 100,000 Population (All Ages) (World - Population Model)*

NIGERIA (Ibadan)	5.8
RHODESIA (Bulawayo)	3.2
CAPE PROVINCE, South African Bantu	11.5
U.S.A. California, Alameda County (Negro)	35.6
JAMAICA, Kingston and St. Andrews	23.5
INDIA, Bombay	10.9
SOUTH AFRICA, Natal Indian	7.6

*Source: Cancer Incidence in Five Continents, Vol. 2, 1970.

TABLE XXXVII

Female White Races: Breast Cancer Incidence Rate Per 100,000 Population (All Ages) (World Population Model)*

U.K., Scotland	58.8
CAPE PROVINCE, South Africa (White)	65.8
U.S.A., California Alameda County(White)	79.6
DENMARK	61.4
HUNGARY, Miskolc	28.8
POLAND, Warsaw City	48.2
U.S.A., Hawaii Chinese	42.0

*Source: Cancer Incidence in Five Continents, Vol. 2, 1970.

TABLE XXXVIII

Male Coloured Races: Breast Cancer Incidence Rate Per 100,000 Population (All Ages) (World - Population Model)*

NIGERIA (Ibadan)	0
RHODESIA, Bulawayo	0.2
CAPE PROVINCE, South African Bantu	0.5
U.S.A., California, Alameda County (Negro)	0.3
JAMAICA, Kingston and St. Andrews	0
INDIA, Bombay	0
SOUTH AFRICA, Natal Indian	0.6

*Source: Cancer Incidence in Five Continents, Vol. 2, 1970.

TABLE XXXIX

Male White Races: Breast Cancer Incidence Rate Per 100,000 Population (All Ages) (World Population Model)*

U.K., Scotland	0.4
CAPE PROVINCE, South Africa (white)	1.4
U.S.A., California Alameda County (white)	0.4
DENMARK	0.5
HUNGARY, Miskolc	0.2
POLAND, Warsaw City	0.4
U.S.A. Hawaii Chinese	0

*Source: Cancer Incidence In Five Continents, Vol. 2, 1970.

These tables show that among the coloured races of the world, the indigens of African origin, Nigerians, Rhodesians, Natal Indians of South Africa and the Bantus of South Africa have about ten times less average annual incidence rate of breast cancer per 100,000 of population than most Europeansand white Americans. All the coloured races of the world have lesser incidence rate of breast cancer compared with most white races. The coloured races here are the Africans, Jamaicans, black Americans and the Indians with dark to light brown skin colours. The Bantus of South Africa and the Indians of Bombay, resident in subtropical zones, have more breast cancer than the African indigens resident in tropical zones. It is of interest here to note that Natal Indians who have migrated from India to South Africa have less breast cancer incidence rate than their counterpart indigens resident in India. It is also of interest to observe that the Jamaicans and black Americans who have migrated originally from tropical Africa to their present environment, particularly the black Americans in the temperate zones, have higher incidence rate of breast cancer than the African indigens resident in the tropics. Among the white races resident in the temperate zones of the world the more affluent and highly industrialised nations of Great Britain (Scotland), American (White), South African (White), and Denmark have two to

three times more incidence rate of breast cancer than the white nations of Hungary, Poland and Hawaii Chinese who are less affluent and less industrialised compared with Great Britain and America. The former group of nations have slightly higher incidence rate of breast cancer than the black Americans resident in America. Lastly, it is pertinent to observe that irrespective of skin colour, all the people resident in affluent and highly industrialised areas of the world have more breast cancer incidence rate than most Africans resident in African countries that are definitely less affluent and scarcely industrialised.

Depending therefore, mainly on skin colour, climate, affluency and degree of industrialisation, in different countries of the world, it may be possible to group the nations of the world with known breast cancer incidence rate into :

(1) High risk Group of Nations

Great Britain,

South African (White),

American (White) and

Denmark.

(2) Intermediate-risk Group of Nations

America (Black),

West Indies,

Hungary,

Poland and

Hawaii Chinese.

(3) Low-risk Group of Nations

Africa - Nigeria & Rhodesia (Black),

Natal Indians (South Africa), and

India.

It is equally observed that for most parts of Africa the relative ratio frequency of breast cancer remains almost the same throughout the continent. Thus in Nigeria the relative ratio frequency of breast cancer is 6 per cent, in Uganda (Davies and Wilson 1954) it is 4 per cent, in French West Africa, (Camain, 1954), 5 per cent and in Ghana (Edington, 1956), it is 5 per cent. These African figures are again lower than the figures quoted by Khanolkar (1961) for India, 8 per cent; Great Britain, 17 per cent, and America, 16 per cent.

It would appear that breast cancer is a disease that afflicts both men and women of the world, with higher proportion accurring in females than in males. This is evidenced by its geographical

and sex distribution in Europe, America, Central Asia, Japan and Africa. However, from the figures quoted above it would seem that the incidence rate and susceptibility to breast cancer in various parts of the world may be (a) Geographically determined as it has been statistically demonstrated that the high risk group of nations as well as the intermediate risk group of nations mostly reside in temperate zones and the low risk group of nations mostly reside in tropical and subtropical zones of the world. (b) May be influenced by geographical migration from one climate to another as has been shown by higher incidence rate of breast cancer in West Indians and black Americans, compared to the less incidence rate for African indigens resident in the tropics. The former group of races have migrated from tropical Africa to West Indies, and temperate zones of America respectively and have adopted the customs and habits of the Europeans and Americans with whom they live. The influence of migration on breast cancer rate is also observed in the Natal Indians of South Africa who have migrated from India to Africa. They have less breast cancer incidence rate than Indians resident in India. It will therefore, appear that people who have migrated out of tropical Africa to other parts of the world may have the effect of environmental factors that seem to increase their degreee of

susceptibility to breast cancer; while the people who have migrated into tropical Africa from other areas of the world seems to have acquired certain environmental factors that seem to decrease their susceptibility to breast cancer. But influence of migration on breast cancer incidence may not be all, for it is observed that the South African whites who have migrated from temperate zones to tropical zones of Africa have still higher incidence rate of breast cancer as their counterpart European indigens resident in Europe and America, and (c) May be racially determined - the race here being solely determined by colour of skin which is due to melanin pigment, for again statistical evidence has shown that breast cancer incidence rate is higher in the white races than in the coloured races of the world. This is in agreement with the observation made long ago by Des Ligneris (1936) that cancer occurs frequently in the black Africans (South Africa Bantus), but not as frequently as in Europeans.

Age Incidence of Breast Cancer:

The mean, median and modal ages of Nigerian females with breast carcinoma in general are 43, 43, and 40 years respectively as compared to the figures of 52.6, 55, and 60 years obtained for the mean, median and modal ages in the males. Nigerian female patients

with breast carcinoma are therefore, much younger than their male counterpart. The Birmingham Annual Cancer Report (1957), reported an average age of English women with breast carcinoma as 55.3 years. Nigerian females with breast cancer are therefore, about 12.3 years younger than their English counterpart. On the other hand, the average age of American male with breast carcinoma is 60 years (Haagensen, 1971) compared with 52.6 years obtained for Nigerian males. American males with breast carcinoma are therefore, about 7.4 years older than their Nigerian counterpart. In Nigeria, 85 per cent of the female patients with breast carcinoma are found in the 30-60 year age-range. This is comparable to the 80 per cent figure quoted by Annamunthodo (1958) for the West Indian women with breast carcinoma in the age-range of 34-64 years, and also with the figure (80 per cent) given by Nathanson and Welch (1936) for American cancer patients in the same age-range of 34-64 years.

SPECIFIC EPIDEMIOLOGICAL STUDY ON 200 BREAST CANCER/CONTROL PATIENTS WITHOUT BREAST CANCER:

The actual cause of breast cancer throughout the world is not yet known. Most European and American authors, as a result of statistical findings based on theories, sound experience on progress of breast cancer and results on experimental animals have authentically proposed numerous, acceptable hypotheses on the aetiology of breast

cancer. In order for the author to provide hypothesis on aetiology of breast cancer, for the first time from tropical Africa, the results based on study of tropical environmental factors on 200 breast cancer/control patients in Nigeria are analysed as follows :

Marital Status

It is gathered from the results of descriptive epidemiology on 200 breast cancer patients that all the carcinoma patients are married. These women usually marry in their teens. This finding is in contrast to the finding on marital status of most European and American women with breast carcinoma, for Rigoni Stern (1842) was the first to observe in Verona that breast carcinoma was more common in unmarried women than married women. Lane-Claypon (1926) later found a higher proportion of Glasgow and London single women in her series of breast cancer patients, than in her series of controls, after studying a variety of features in series of 508 women with breast carcinoma from Glasgow and London hospitals and 509 controls. In view of all these, it is doubtful whether marital status of a woman in Nigeria has any part to play in development of breast carcinoma for both the cancer patients and the controls in this series are married.

Environment, Occupations and Diet Habits:

Both the cancer and control patients belong to the low socio-economic group. Because most of them are farmers they worked in tropical, dusty, hot and dry environment with high relative humidity. They all thrive mainly on high carbohydrate and low protein diets, but tend to consume large quantities of green vegetables of various types. The European and American women on the other hand, are more affluent, have a higher standard of living and work and live in the temperate zones of the world. Because of their cold weather, all these nations spend all their lives to keep warm with coal fires or electric and gas heaters. While the African women tend to consume vegetables and fruits mostly matured and rippened naturally, most European and American women on the other hand, tend to liver on food stuffs mostly preserved by chemicals, (personal observations). The African women do consume a lot of unsaturated vegetable fats from palm oil, ground-nut, and coco-nut, oils, while most European and American women on the other hand tend to consume a lot of saturated animal fat such as butter, milk and animal cooking fat. The African women cook with dry woods of various types, and kerosene stoves that may be possible sources of polycyclichydrocarbons, which Bonser and Orr (1939) had earlier used to induce mammary

cancer in virus free female mice. Though the European and American women cook mainly with gas and electricity, they do live in highly industrialised areas of the world where air pollution with petroleum fumes and industrial gases is extremely high. From the result of the study on incidence rate of breast carcinoma per 100,000 population, Doll, Muir and Waterhouse (1970) it has been shown that both the Europeans and the Americans have a high incidence rate of breast carcinoma than the Africans, the former group of nations belonging to the High-risk Group and the latter to the Low-risk Group. These European and American females that have higher incidence rate of breast cancer, tend to be more affluent than African women. They are in higher socio-economic brackets than their African counterpart. Thus, apart from skin colour, state of affluency, climate, diet, occupation and social customs of various nations of the world, may contribute to the aetiology of breast cancer. These factors may equally add to other factors responsible for the higher degree of susceptibility to breast cancer observed in most European and American women than in most African women.

De Waard (1969) had suggested that the post-menopausal cancer in white women of America may be due to over-nutrition, which induces over-weight and increase in the secretion of adrenocortical hormones.

Drug Habits:

On drug habits, the Nigerian patients, sometimes in their lives might have used "AGUNMU" and "AGBO" concoctions prescribed for them by the native doctors. It is also possible that their staple diets of rice, beans and ground-nuts, on storage, may sometimes be contaminated by the mould Aspergillus flavus from which aflatoxin is extracted. Both the concoctions and the mouldy stored rice, beans, and ground-nuts have been shown to contain aflatoxin (Bassir, 1977). Alcroft and Carnaghan (1962) have shown that cows fed on ground-nuts contaminated by aflatoxin secrete the latter in their milk which is toxic to ducklings fed with the milk. Butler (1966) has suggested that apart from the liver, aflatoxin may be a factor in the aetiology of cancer in other organs of animals. A leading article in the British Medical Journal (1964) has drawn attention to the possible hazard to human health that may result from the consumption of food contaminated by aflatoxin. Aflatoxin is a known carcinogen of natural origin and a known powerful hepatocellular carcinogen which may well be responsible for some of the primary human liver cell cancer which is indeed prevalent amongst young Nigerians. What aetiological role aflatoxin may play in development of breast carcinoma in Nigeria where ground-nuts, beans and rice may

occasionally be contaminated by the mould, Aspergillus flavus, is speculative and, indeed, needs investigation. The problem of the "Pill" most commonly used by most European and American women does not appear to arise in Nigerian rural areas in the past, but the modern Nigerian women do commonly cunsume these tablets nowadays like most European and American women. It has not yet been proved that the "Pill" has carcinogenic effect on mammary glands. But it is well known that oestrogen is the hormone that determines the sex difference seen in the growth and size of breast during puberty. The ovarian oestrogen starts to act on female breasts from puberty until menopause. The oestrogenic effect on female breasts are periodically marked during menarche, menstruation and pregnancy. Because of the well known fact that oestrogen causes proliferation of the peithelial cells of the mammary glands, there was an early focus of attention on the relationship between ovarian oestrogen and breast carcinoma. Thus Lacassagne (1933) was the first to induce carcinoma of the breast in three male mice of the R III Strain, by treating them with oestrogen. This experimental production of mammary carcinoma with oestrogen or its derivatives in laboratory animals, was subsequently carried out by Bonser (1936), by Haagensen and Randall (1945), and by Hall and Moore (1966). The

carcinogenic effect of oestrogen on breasts has also been observed in humans. Thus McClure and Higgins (1951) reported a case of bilateral carcinoma in a male breast after oestrogen therapy. A year later, Jakobsen (1952) reported a case of mammary carcinoma in a male following stilboestrol therapy. Symmers (1968) also reported occasional cases of men who in the process of undergoing artificial sex change have received large does of oestrogen in order to produce enlargement of breast, and subsequently developed breast carcinoma. Moreover, Herrell (1937), and Feinleib (1968) have both respectively shown that oophorectomy appears to lower the incidence of subsequent development of breast carcinoma in such treated women. There is therefore, no doubt that oestrogenic hormones may play a prominent role in the aetiology of breast cancer in human beings. Lemon, Wotiz, and Parson (1966) proposed that women predisposed to breast cancer have a genetically determined impaired hydroxylation of estrone and estrodiol to estiol by hydroxylases of the liver and the gut. Supporting this hypothesis MacMahon, Cole, and Brown (1973) showed that there is a considerable higher estriol ratio in population of Asia with low risk of breast cancer than those in North America with a high risk of breast cancer. As a result of this it is suggested that the excessive carcinogenic effect of

oestrogen in human breasts, may be expressed more commonly in female, than in male, breasts, and this may solely be responsible for higher incidence rate of breast carcinoma observed in females than in males through out the world.

Fertility:

In the group of 200 breast carcinoma patients studied, 9 patients are barren, while all the 200 control patients are fertile. The carcinoma patients tend to have fewer pregnancies than the controls, (921 pregnancies for the patients as against 1,092, for the controls); also the carcinoma patients tend to have fewer living children than the controls, (535 living children for patients as against 682, for the controls). A carcinoma patient has an average of 2.68 living children. While a control patient has an average of 3.41 living children. The carcinoma patients tend to have more dead children than the control patients. A carcinoma patient has an average of 1.59 dead children as compared with the control average of 1.43 dead children. The average number of miscarriages per carcinoma patient is 0.59 and that of the control is 0.57. These figures show that the average number of dead children per female is highest in the carcinoma patients than in the control patients. The same observation holds for the average number of miscarriages per female. The difference of the

two ratios for the groups is not statistically significant. Van des Warff (1956) of Belgium found that single women and married women without children have more breast cancer than women with children. MacMahon (1958) studied a series of American women and found a definite decrease in the incidence rate of breast carcinoma with rise in number of gravida of women he studied. Gillian (1951) after studying series of breast carcinoma patients in New York, Missouri, and New Orlean hospitals, found that cancer patients have fewer pregnancies, and fewer live births than women in the general population. Shartz, Denoix and Rouquette (1958) reported similar observation on the group of French women they studied and noted that cancer patients had fewer children than their controls. The current findings in Nigeria appear therefore, to be in agreement with the findings in Belgium, America and France. From all these, it is being suggested that pregnancy, fertility, emotional upset induced in women by death of their children in peurperium, stillbirth or by foetal wastages in miscarriages may have an important role to play in the aetiology of breast carcinoma in women of all races.

Breast Feeding:

The role of breast feeding in development of breast carcinoma in women is important and must be considered objectively. Ninety-four (94) per cent of the carcinoma, and 98 per cent of the control,

patients, breast fed all their children. These figures are comparable with the figures obtained by Hirayama and Wynder (1962) for Japanese women. They showed that 96 per cent of Japanese women with breast cancer, and 97 per cent of the control group did nurse their babies. Here in Nigeria each carcinoma patient breast fed an average of 3.1 children while each control patient breast fed an average of 4.1 children. The carcinoma, and the control patients spent on the average 2.5 years breast feeding a child. There is therefore, no difference in the pattern of breast feeding between the two groups. In Glasgow and London, Layne-Claypon (1926), after studying 213 breast carcinoma patients with similar control patients from Glasgow and London Hospitals, showed that 14.6 per cent of the children in her cancer series, and 7.4 per cent of the control children, did not breast feed. Wainright (1931) showed that in New York and Pennsylvania, 28.2 per cent of the American married women in her cancer series and 15.7 per cent of the control women did not nurse their children. Gerard (1970), observed that only 3 per cent of American women in the American metropolitan areas today, nursed their babies for as long as 6 months, in contrast with Nigeria where an average mother spends at least 2.5 years nursing a child. The analysis of annual incidence rate of breast carcinoma, for all

ages, per 100,000 of female population obtained from Cancer Incidence In Five Continents, (Doll, Muir and Waterhouse, 1970), has shown that white American women in California, Alameda County have breast cancer incidence rate of 79.6 per 100,000 for all ages and the Scottish women 58.8 per 100,000. These two nations are noted for artificial bottle feeding rather than breast feeding their children. On the other hand, the incidence rate of breast carcinoma for Nigerian women is 5.8 per 100,000 and that of Japanese women is 10.5 per 100,000. These two nations are noted for high incidence of breast feeding their children. Since the former group of nations, who are noted for artificially feeding their children with variants of cow's milk, have more breast cancer incidence rate per 100,000 of population, than the latter group of nations, who are noted for breast feeding their children naturally, it does strongly appear, that, on the whole, breast feeding may protect these nations against developing more breast carcinoma or in reducing their risk of developing as much breast cancer as most European and American races who seldom breast feed their children. The author therefore, agrees with Haagensen (1971) who after studying the relationship between breast cancer and breast feeding in American women declared that in ethnic groups of the world, breast feeding may appear to protect women

against developing breast cancer.

Melanin Pigmentation and Breast Cancer

From the currently analysed evidence on the incidence rate of breast cancer, the following facts have emerged :

1. Breast cancer occurs in all races of the world, but its incidence is higher in the white races than in the coloured races.

2. Among the coloured races the incidence rate is higher in the Indians with light brown skin colour than in the African races with black skin colour. It is adduced from this that the deeper the skin colour the lesser the incidence rate of breast cancer.

3. Among the coloured races it is also observed that:

   (a) The West Indians and the black Americans whose ancestors had migrated from tropical Africa, to West Indies, and to temperate zone of America, respectively have more breast cancer incidence rate than the African indigens.

   (b) The Natal Indians on the other hand, who had migrated to Africa adapted themselves to tropical environment have less breast cancer incidence rate than the Indians in India.

The important question that arises from all these observed facts is : "Does the absence of skin pigment (melanin pigment) predispose the white races to development of more breast cancer than the coloured races ?"

It is observed that the only obvious difference between the races of the world is the colour of the skin which is determined by the degree of melanin pigment present in the skin. Toda,, Pathak, Fitzpatrick, Quevedo, Morikawa and Nakayama (1973) have shown that the only difference between the white skin and the coloured skin is that in the white skin the melanin granules are scanty while in the black skin they are abundant. There is also observed difference in distribution pattern of melanin granules in the epidermal cells of both white, and coloured skin. Using the electron microscope the authors also showed that in the caucasoids, Americans, Indians, and Mongoloids, usually groups of two or more melanosomes or melanin granules are found in the epidermal keratinocytes bound in a unit membrane. In the Negroids and the Australian aborigines, on the other hand, they found that the melanosomes are usually non-aggregated (single) and are diffusely scattered in the cytoplasm of the epidermal keratinocytes. It is also a well known fact that a black body absorbs heat much better than other coloured bodies. Melanin pigments are

black, and from their distribution patterns in both races described above, it may be inferred that the black skin is well equipped for absorption of solar rays more than the white skin, and thereby can effectively shield the nucleus from the harmful effects of solar rays.

Coming now to answer the question above, the following theoretical evidence has been put forward to show that melanin pigmentation may play a protective role against the carcinogenic effects of solar radiation or other types of carcinogens :

(1) Watkins-Pitchford (1910) was the first to infer "that blonde varieties of man and other animals are more liable to cancer than their pigmented congeners, suggested that such pigmentary deficiency might constitute a form of 'stress'. He further stressed that "pigmentation usually connotes illumination, and the obvious association of certain forms of cancer in the white man with prolonged exposure to radiant stimulation seemed to lend a support to his hypothesis that the absence of effective pigmentation or other form of external protection in the white man is the primary cause of his liability to cancer."

(2) <u>Evidence from Animals</u> -

(a) Watkins-Pitchford was quick to point out to the critics on his essay on "Light, Pigmentation, and New growth

"the white and grey horses have special liabilities to cutaneous sarcoma, the Angola goats to cancer of anus and vulva, and the white man (as contrasted with the black man who live in Natal and Zululand), to cancer of all forms."

(b) Sixty-three (63) years later, Rose (1973), in his article on "Pigment Variation in Relation to Cancer" cited a personal communication he received from Professor J. Bonsma (1973) of the Pretoria University stating that he (the Professor) had found a high incidence of cancer and ophthalmia round the eyes of white-faced Hereford cattle. This, he believed, was related to amount of pigment. By selective breeding the Professor was enabled to observe increased pigmentation around the eyes of the animals and a reduction in the incidence of cancer and ophthalmia in these animals. He concluded from this observation that white-faced Hereford cattle lacking pigmentation round the eyes are more susceptible to cancer and ophthalmia than those cattles with pigments round their eyes.

(3) Evidence from Sole of Foot:

Generally in black races the palm of the hand and the sole of the foot are not normally pigmented. Booher and Pack

(1957) had earlier observed that when malignant melanoma occurs in American negro, it frequently develops in a relatively non-pigmented areas of skin such as the sole of foot. The current author from the department of Pathology University Teaching Hospital here, has diagnosed maligaant melanoaaa that was excised from the sole of foot of three black Nigerian male patients (unpublished).

(4) Evidence from Depigmented Skin -

The epithelium covering the white scars of old burns (depigmented areas) is prone to become cancerous, Watkins-Pitchford (1910).

(5) Evidence from Albino Studies -

(a) Watkins-Pitchford (1910) long ago made the following remark: "After deligent enquiry I am assured that the only one native of Natal has been known to the present generation of practitioners to have suffered from rodent ulcer. This native is an albino!"

(b) In Nigeria it is only albinos that are usually observed to develop rodent ulcer in the face. The author has personally, made a histological diagnosis of squamous cell carcinoma of the face that had invaded the right maxillary sinus, and required a commando operation, in a Nigerian albino (unpublished).

(c) Albinism however, is usually inherited as an autosomal recessive characteristic. In adult albinos the presence on the exposed part of keratosis, and squamous cell-carcinoma and basal-cell carcinomata emphasises the importance of melanin as a protective agent, Walter and Israel (1974).

(d) Rose (1973) recently remarked that the high incidence of skin cancer observed in the white races of South Africa may tend to substantiate the theory that pigmentation plays a protective role against carcinogenic effects of radiation, Watkins-Pitchford (1910).

All these evidence tend to point out to the fact that melanin may play a protective role against the development of skin cancer irrespective of the aetiology. The skin and the breast have the following in common :

(1) Both develop-mentally, are derived from the ectoderm of the embryo.

(2) Both organs are mainly the most exposed areas of the body, although the skin covers the mammary glands externally.

Is it then possible, to state that melanin pigments may offer protection to breast glands against carcinogenic effects of solar

radiationoor any other type of carcinogenic agent, as it offers the skin? If the answer is in the affirmative, then it may be possible to postulate the following :

The coloured races of the world have inherited the gift of melanin pigmentation for protection against not only the solar rays, but also against the carcinogenic effects of solar radiation. It is therefore, being suggested that the white races may have more skin and breast cancer (both organs being of ectodermal origin) than the coloured races because their ectodermal cells (melanophores) have not inherited as much ability to synthesize melanin granules as seen in the coloured races, to protect them against the carcinogenic effects of ultra-violet rays or other forms of radiation.

The genetic factor in the melanin pigment appears to show some variation in its degree of penetrance and expression. It has a high degree of penetrance and expression in the pure black races, and low degree in the light brown-coloured Indians, and in the so called "black Americans" who are usually composed of a mixture of black people and mulatoes "quadrons" and "mustees" that are socially and statistically grouped together in the United States as "Blacks" Watkins-Pitchford, (1910).

This may be a valid point for it is observed that breast cancer incidence rate in "black Americans" (mixed coloured races) is higher than those of pure black African races; and that of the Indian races (light-brown coloured races) is also higher than that of the black African races.

There is of course, no actual experimental evidence to show that melanin indeed, protects against cancer, for this reason it is being recommended that a deeper study should be carried out on the abnormalities of melanin pigment and histogenesis of cancer. The studies on these striking differences, such as exposure to environmental factors and genetically determined "melanin pigment" factor, observed between the coloured and white races of the world may lead nearer to the understanding of aetiology of cancer, particularly, breast cancer, throughout the world.

Relationship of Benign to Malignant Breast Lesions:

The question confronting one here is : "DOES ANY KNOWN MAMMARY BENIGN LESION PREDISPOSE THE AFFLICTED BREAST TO CANCER ?

The following is presented in an attempt to answer this question.

(1) **Infective and Non-Infective Benign Lesions** -

The causative agents of most infective mammary lesions such as tuberculosis, schistosomiasis, onchocerciasis and unresolved mammary abscesses are known throughout the world. None of these conditions is known to predispose the afflic ted breast to malignancy. All of them however, along with fat necrosis of breast, may result in formation of hard immobile mammary lumps with associated dystrophic calcification. Their importance in the tropics lies in the fact, that breast lumps resulting from them can clinically, in all aspects, mimick breast carcinoma. In the tropics therefore, it is strongly recommended that all breasts lumps should be excised and examined histologically to exclude these treatable benign conditions before any radical surgery on the breast is contemplated by the clinicians.

(2) **Fibroadenoma and Breast Cancer** -

Fibroadenoma is the commonest benign tumour of young female Nigerians. It starts occurring in the females at menarche and reaches

its peak in the 22-25 year, age-group women and thereafter declines to become non-existent in the menopausal and post-menopausal women.

The aetiology of fibroadenoma is attributed to hormonal imbalance, particularly oestrogen. As has already been stated in this study, oetrogen was first used by Lacassagne (1933) to induce mammary carcinoma in experimental male mice. This had been subsequently confirmed by Bonser (1936), by Haagensen and Randall (1945), and by Hall and Moore (1966). In the human cases, McClure and Higgins (1951), Jakobsen (1952) and Symmers (1968) respectively reported cases of male breast carcinoma caused by prolonged therapy with oestrogen or its derivatives for certain male lesions as has already been explained earlier in this thesis.

In general, the epithelial component of fibroadenoma is often subjected to the same oestrogenic stimulus as the mammary gland epithelial cells. Is it then possible to speculate that occasionally carcinoma may originate within fibroadenoma?

Semb (1928), had earlier followed up one-hundred and twenty-four (124) cases of fibroadenoma for up to 4-27 years and reported that he did not find a single instance of development of carcinoma in any of his cases. Foote and Stewart (1945), on the other hand, had

made it clear that malignant fibroadenomas are the rarest of all malignant neoplasms of the breast; and that when the common intracanalicular fibroadenoma udergoes a malignant change, it is usually the epithelial portion that is involved rather than the connective tissue. This latter view was later confirmed by McDivitt, Stewart and Farrow (1967), and by Goldman and Freidman (1969) when they reported 13 cases and 3 cases, respectively of lobular carcinoma in situ arising within bening fibroadenoma. **Haagensen (1971), on the** other hand, did not find a single malignant growth developing exclusively within an adenofibroma, (fibroadenoma) in his long experience of studying breast diseases. However, after reviewing one-hundred-and-twenty-four (124) cases of fibroadenoma in the current study, only a single case of secretory (juvenile) carcinoma was discovered developing within an intracanalicular fibroadenoma, in a 20-year old Nigerian female.

Secretory (juvenile) carcinoma of the breast is rare even in the Western world. McDivitt and Stewart (1966), were the first to report this distinctive rare breast carcinoma that occurred in childhood. They showed that these tumours have characteristic morphology, and according to them an indolent clinical behaviour. They reported a study of 6 cases over a period of 15 years in children ranging in age from

three to fifteen years. All the carcinomas had similar histological appearance with abundant secretion in the cytoplasm of the tumour cells and in the glandular spaces formed by these cells. In a survey of 5,000 cases of breast carcinoma from the Armed Forces Institute of Pathology, Norris and Taylor (1970) reported 135 cases of the carcinomas in women less than 30 years old. Six of these latter cases were juvenile secretory carcinoma. All the patients were mainly between 20 and 30 years of age, but one was 10 years old. The current study has now reported for the first time in history of Africa a case of secretory (juvenile) breast carcinoma evolving from the epithelial component of pericanalicular fibroadenoma, in a 20-year old Nigerian woman.

This current African finding, therefore, appears to fulfil the dictum enunciated long ago by Foote and Stewart (1945) as has been stated above. It also appears that there may be a geographical difference between the tropical and temperate zones as regards the histological type of malignant epithelial lesion that can develop within a fibroadenoma. Only a single case of secretory (juvenile) carcinoma superimposing an intracanalicular fibroadenoma is discovered within the 16-year period of this study. Since then, the author from the department of Pathology here, has however, diagnosed two other

cases of secretory carcinoma within pericanalicular fibroadenoma in young Nigerian females (unpublished). Although this may be an insufficient evidence, it would seem that in Africa (Nigeria) secretory carcinoma might be found occasionally developing within pericanalicular fibroadenoma more often than any other histological type of breast cancer diagnosed locally. This finding would appear to be in contrast to the finding of lobular carcinoma in situ developing occasionally within intracanalicular fibroadenoma as had been discribed in American females by McDivitt, Stewart and Farrow (1967) and by Goldman and Friedman (1969).

(3) Malignant Giant Fibroadenoma -

It is well known that giant fibroadenoma is a fibroepithelial tumour often derived from intracanalicular fibroadenoma. It is a benign tumour which may sometimes undergo malignant change either to a sarcoma or to a carcinoma, as has been well documented by Treves and Sunderland (1951), by Norris and Taylor (1967) and by Haagensen (1971). The latter author found typical lobular carcinoma in situ in close association with cystosarcoma (giant fibroadenoma) in four cases he reported. In two of his cases, he observed the lobular carcinoma in situ localised entirely within the lesion, while in others it was seen in different areas within the tumour.

Out of the ten female and two male, cases of giant fibroadenoma reviewed in this study only one case of malignant giant fibroadenoma was discovered. This is a case in which a fibrosarcoma was seen developing in the fibrous stroma of the benign lesion of a 45-year old Nigerian female patient. It is agreed that with most European and American authors that benign giant fibroadenoma of breast, can sometimes undergo malignant change either to a sarcoma or to a carcinoma.

(4) Gynaecomastia and Breast Cancer -

The hormonal mechanism responsible for pubertal gynaecomastia is not clearly known, but Collet-Solberg and Grumbach (1965) were able to indentify a greater oestrogenic effect in urine cystograms in boys with pubertal gynaecomastia. They suggested that this might be due to a delay in the reversal of the androtenedione-testosterone ratio that normally oucurs at puberty.

It is well known that gynaecomastia occurs within a variety of different types of developmental abnormality of testes, such as cryptorchidism and hypospadiasis, Haagensen (1971). Klinefelters syndrome, a 47, XXy chromosomal anomaly, a syndrome occurring in about 1 in 500 male births, is often associated with gynaecomastia - Walter and Israel (1974). In Nigeria none of the gynaecomastic lesions

reviewed is associated with any of the above anomalies, but they do occur. None of them also is associated with cirrhosis of the liver or Kwarshiorkor. However, the question is : Can gynaecomastia undergo malignant change?

Karsner (1946), Huggens and Taylor (1955), Treves and Holleb (1955) and Sirtori and Veronesi (1957) all made it clear that cancer of breast rarely supervenes on gynaecomastia. Norris and Taylor (1969) after their extensive study on carcinoma of male breast declared that most mammary cancers develop in men with either non existent or quiescent gynaecomastia. But from Africa, Edington (1956) on the other hand, suggested that breast cancer in males would appear to be relatively more common in the Gold Coast (Ghana) than in Europe, the aetiological agent in its production perhaps being gynaecomastia, a not uncommon finding in malnutrition and cirrhosis of the liver over there. This current study (Nigeria) has shown no evidence to substantiate Edington's (1956) latter observation in Ghana. Haagensen (1971), however, rpporting on senescent mammary hypertrophy (adult gynaecomastia) suspected that there might be some association between senescent hypertrophy and carcinoma of the male breast but because he found that male breast carcinoma was so infrequent in America, he could not provide any statistical support for his thesis.

He however, went on to describe a case in a 51-year old man in whom senescent hypertrophy was associated with carcinoma of breast. The current study, has reported only a single case of intraductal papillary carcinoma with cart-wheel pattern, developing within a gynaecomastic lesion in a 38-year old Nigerian male. This is definitely not sufficient to conclude that carcinoma may or may not supervene on benign gynaecomastia. It is, however, believed that this may occur, as epitherliosis and papillomatosis have been currently observed in gynaecomastia. This latter changes that are often observed in fibrocystic disease of female breast are strongly believed to be precancerous conditions, Willis (1960) and Sandison (1962).

(5) Fibrocystic Disease and Breast Cancer -

Fibrocystic disease of breast does not seem to be clinically evident until some years after the ovarian fuction is established. This perhaps, may be the reason it subsides and disappears with menopause when the ovaries become atrophic. It is a benign mammary lesion that frequently involves both breasts. As for its aetiology, it has been suggested that fibrocystic disease, in some way, may be an expression of an abnormal ovarian function which may be due to excess oestrogen or some other hormonal dysfunction (Haagensen, 1971).

Evidence has accumulated in the literature to show that administration of excess oestrogen to experimental animals such as mice, can lead to epithelial hyperplasia of the animal's mammary glands, Haagensen and Randall (1942). However, Engle, Krakower and Haagensen (1943) were able to produce cystic changes, but not epithelial hyperplasia in Rhesus monkeys they treated with oestrogen.

In man, both European and American authors have for centuries focused their attention on the possibility of relationship between benign fibrocystic disease of breast, and mammary carcinoma. Thus Astley Cooper (1845), writing on the anatomy and diseases of the breast, recorded the coexistence of cystic disease and carcinoma. Greenough and Hartwell (1903) showed that 10 per cent of their 30 cases of cystic disease, "Senile parenchymatous hypertrophy" had carcinoma and regarded the adenocystic form as precancerous. They considered carcinoma to develop no more frequently in this condition than in the normal breast. MaCarty and Mensing (1915) stated that carcinoma of the breast is always associated with chronic mastitis. Fischer (1925) had concluded that in the vicinity of carcinoma various gradations of cystic disease are often found, and that the lesions might have the same genesis. Semb (1928) provided specific data on frequency with which breast removed for carcinoma show gross cystic disease. In a

series of 22 cancerous breasts, he found in 27 per cent of cases, grossly visible cysts which he termed fibroadenomatosis cystica simplex. Cheatle and Cutler (1931) maintained that 20 per cent of cases of breast carcinoma arose on the basis of cystipherous desquamative epithelial hyperplasia. Muir (1941), in Scotland, showed many illustrations of the histological changes in breast lesions from benign hyperplasia to carcinoma in 11 patients. Foote and Stewart (1945) in America found grossly visible cysts in 27 per cent in their series of 300 cancerous breasts. Haagensen (1956) found that of 713 patients with breast carcinoma, 176 or 24.7 per cent had grossly visible cysts. Willis (1960) in his text book on Pathology of Tumours has exphasised that "the more thoroughly the pathologist examines amputated breasts, the more often will he discover the presence of cystic hyperplasia in association with carcinoma and of clear transition from one to the other". Recently Devitt (1972), and MacMahon, Cole and Brown (1973) respectively found that in approximately 5 per cent of women with breast cancer, prior biopsy specimens were reported as showing fibrocystic disease. Silverberg, Chitale, and Levitt (1972), reported that 20 to 40 per cent of breast removed for carcinoma also show fibrocystic disease.

Histologically, Davis and Simons (1964) enumerated various histological types of breast carcinoma they found associated with cystic disease in their 327 patients with carcinoma. These include infiltrating papillary carcinoma, comedo-carcinoma, scirrhous carcinoma, medullary carcinoma, colloid carcinoma and infiltrating lobular carcinoma. They studied the three most common types of carcinoma to discover the frequency of associated benign intraductal hyperplasia frequently seen in fibrocystic disease. They discovered that:-

(1) Only 6 cases (4.2 per cent) of 143 cases with scirrhous carcinoma.

(2) 21 cases (20.2 per cent) of comedo-carcinoma.

and (3) 13 cases (29.5 per cent) of 44 cases of papillary carcinoma

had associated benign hyperplasia. They concluded that pure scirrhous carcinoma is rarely associated with cystic disease, and that there was a more frequent combination of benign intraductal epithelial hyperplasia with comedo-carcinoma and the papillary types of carcinoma. The histological types of breast carcinomas associated with fibrocystic disease reported in the current study are similar to those reported by Davis, Simons and Davis (1964), for it was observed that 87 per cent

of all the intraductal carcinoma, 67 per cent of all the lobular carcinomas (invasive), 22 per cent of all the papillary carcinomas and 20 per cent of all the carcinomas with diffuse fibrosis (scirrhous) carcinoma, are associated with fibrocystic disease, scirrhous carcinoma being the least. Thus in both Davies, Simons and Davis (1964) and the author's series, scirrhous carcinoma is least commonly associated with benign fibrocystic disease when compared with other histological types of breast carcinoma. Moreover, it has also been observed that 99 cases (24 per cent) of breasts amputated for carcinoma are found to have associated fibrocystic disease in the adjoining breast tissue.

The correlation coefficient calculations carried out in this study have shown that there is evidence of positive linear association between (1) fibrocystic disease alone (X_1) and fibrocystic disease associated with carcinoma (X_2), and also between (2) fibrocystic disease associated with carcinoma (X_2) and carcinoma alone (X_3). The result of chi-squared test has also provided a very strong evidence that fibrocystic disease alone, and fibrocystic disease associated with carcinoma are related to age. The average age of patients with fibrocystic disease alone (X_1) (31 years), is years lower than the average of 41 years obtained for patients with fibrocystic disease

associated with carcinoma ($\bar{x}_2$). The latter group of patients falls into cancer age-group of most patients in this community.

The result of this current study has therefore, enabled the author to unquestionably, agree with Muir (1941), Willis (1960), Sandison (1962) and many other pathologists that cystic hyperplasia has precancerous potentialities. It may be that both conditions when present in one breast lesion may have common aetiology. This common aetiological factor may primarily initiate fibrocystic disease that show areas of epitheliosis which Sandison (1962) maintains is the key pathological change in cystic mastopathy. He further maintains that sometimes gradation from papillary epithelial hyperplasis through papillomatosis to frank papilloma may be observed in cystic-mastopathy. Although there is considerable debate on the question, the general consensus is that epithelial hyperplasia is sometimes a precancerous condition, Willis (1960), Sandison (1962). In spite of this, McDivitt (1978) in his recent vreview article on breast carcinoma still maintains that "one might wish to assume that there is some relationship between fibrocystic disease and carcinoma even though it has not been adequately demonstrated, but atill he would hesitate to support this point of view.

Pathology of Breast Cancer in Nigeria:

The progress in the study of cancer in most parts of developing Africa is bewildered with so much problems and difficulties that are inevitably very challenging. It is therefore necessary from the start of this chapter to draw attention to some of these problems and difficulties, a modern doctor in this part of developing Africa, Nigeria, may often encounter :

(1) There is absolute mass ignorance on nature of cancer as an important disease that causes death, particularly in most rural areas of Nigeria.

(2) The "native doctors", even today, do still exert powerful influence over most patients in Nigerian rural areas. They are often the first choice of "healers" to be consulted by such patients with any form of disease. As a result of this, there is always an inevitable delay before such patients seek medical aid in a modern hospital. The modern Nigerian clinicians are therefore, often confronted with rather advanced fungating mammary lesions as shown in photographs 2 and 5. In some cases, an occasional patient may present with cancer that has caused autoamputation of the breast (photograph 1).

(3) In a developing country, such as Nigeria, there are inadequate number of hospitals, inadequate hospital facilities, and inadequate number of hospital personnel that make the task of health care delivery by modern doctors almost seem impossible. In addition to these, it is observed that the few available modern hospitals are usually concentrated in the big cities. Consequently, most Nigerian rural areas that are remote from such hospitals, due to inadequate transport facilities, do find the latter inaccessible.

These are some of the reasons that may be responsible for delays and inaccurate prolonged duration of symptoms of breast cancer encountered in Nigeria. In contrast, most European and American countries are far advanced in all aspects of life compared with all the developing African countries. While the European and American clinicians are busy today, intensively searching for the aetiology of breast cancer and diagnosing and treating mammary carcinoma in situ, the modern African clinicians, on the other hand, are still having the unique opportunity of observing the natural history of breast cancer.

Classification of Breast Cancer:

In adopting the classification of breast carcinoma originally proposed by Foote and Stewart (1946) and subseqeuntly adopted by McDivitt, Stewart and Berg (1968) and recently modified by Pathology Working Group, Breast Cancer Task Force, National Cancer Institute of America (1973), it is believed that the classification is complete, meaningful, and reproducible, and can easily permit international comparison of various histological types of breast cancer found in the tropics with those found in the temperate zones.

The various histological types of breast cancer found in Nigeria has been classified, grouped, and sub-grouped according to this international recommendation. In adopting the internationally accepted nomenclature of various histological types of breast cancer, it has been observed that most histological types of breast cancer found in Africa (Nigeria) are in no way different from those occurring in the other parts of the world. What is observed though, is that, histologically, breast cancer is just not a single disease, but a group of diseases affecting one organ, the BREAST. It is a disease composed of different histological types of cancer, each having its own peculiar histological features and biological behavioural pattern that helps its identity. Of all the histological types, the only exceptions that were not diagnosed in the series are :

(1) Signet-ring carcinoma (Group I, B.13)

(2) Breast carcinoma with granular cells (Group I, B. 15)

(3) Adenoid cyst carcinoma (Group I, C. 2)

(4) Malignant mixed salivary gland tumour (Group I, C. 3)

(5) All the sub-groups of neoplasms of epithelial origin (Group II, A)

These include (a) squamous cell carcinoma (Group II, A. 1), (b) basal cell carcinoma (Group II, A. 2), (c) eccrine seat gland carcinoma (Group II, A. 3) and (d) malignant melanoma (Group II, A. 4). This does not however mean that they may not occur in Nigerian breast lesions, but apparently, they are rather rare, especially when it is recalled that basal cell carcinoma and malignant melanoma are amongst the rarest types of skin malignancy that can generally occur in deeply pigmented African skin. It may be pointed out here, that primary squamous cell carcinoma arising from the mammary glands does occur but is rare, and in most cases it may not be easy to differentiate this type of tumour from carcinoma of breast with squamous metaplasia.

Lastly, (6) Angiosarcoma (Group II, B. 1), rhabdomyosarcoma (Group II, B. 3) are granular cell myoblastoma (Group II, B. 4).

For clinical purposes it was necessary to group the various histological types of breast carcinoma into two broad groups following

the teaching of Haagensen (1971). These are :

(1) The 8 common histological types of female breast carcinoma, that have been already enumerated in table XVIII on page 52.

and (2) The rare histological types of female breast neoplasia in table XIX, at page 54.

All the histological types of breast cancer belonging to the group of "common histological types" are mainly neoplasms of ductal epithelial origin, except lobular carcinoma which is a neoplasm of lobular epithelial origin. On the other hand, all the histological types belonging to the "rare histological types", are indeed rare in Nigeria as elsewhere in the world. They are composed of various classified histological types drawn from both Groups I and II. The low percentage incidence of lobular carcinoma in situ recorded in this group may be due to the fact that this type of neoplasia is only diagnosed histologically, and not clinically, and as such the Nigerian pathologists and surgeons alike did not pay much attention to its existence. The ones described here were discovered by chance, after reviewing the slides diagnosed as fibrocystic disease.

The histological types of male breast malignant neoplasia shown in table XX, at page 55, consists of a combination of both the

"common" and "rare" histological types equally found in females; but because they are few in number they are put together in a table.

The two histological types marked (*) and included under the (sub-group I, B) are not internationally recognised, and have neither received international nomenclature nor classification. They are included here to complete the various histological types of breast cancer seen in Africa (Nigeria), for the following reasons:

(1) They are all histological types of breast carcinoma derived from mammary ductal epithelial cells.

(2) * Medullary carcinoma with polymorpho-nuclear leucocytic infiltration (Group I, B. 7b.)

On reviewing the slides on medullary carcinoma (see page 94) it was found that this commonest histological type of breast cancer in Nigeria, is composed of three histological types, depending on the type of predominant host cellular reaction to their presence. The international sub-classification of medullary carcinoma into (Group I, B.7) and (Group I, B. 7a), is based solely on whether the medullary carcinoma is accompanied by a particular host cellular reaction, lympho/plasma cells or not. It has been discovered that in Nigeria, medullary carcinoma may constantly be distinguished into three main sub-types by the presence, or absence, of not only lympho/plasma

cells but also by the presence or absence of polymorpho-nuclear leucocytes as the main host cellular reaction. Depending, therefore, on the type of predominant host cellular reaction, medullary carcinoma found in Nigeria has been sub-classified into :

(a) Medullary carcinoma with lympho/plasma cell infilration (Group I, B. 7a).

(b) Medullary carcinoma with polymorpho-nuclear leucocytic infiltration (Groupl, B. 7b).

and (c) Medullary carcinoma with neither lympho/plasma cell nor polymorpho-nuclear leucocytic infilration (Group I, B. 7c). For further details (see page 94).

(3) *Carcinoma of breast with composite histological structures.

Ten (10) cases, two per cent (2%) of the breast malignant lesions in the current Nigerian series can not be fitted into any of the internationally recognised histological types of breast malignant neoplasia as classified above. These are cases in which sections obtained from a breast lesion contains various histological types of tumour, either in the same section, or in different sections obtained from different sectors of the same tumour. They have been included amongst the classified types of breast carcinoma found in Nigerian patients as they form a definite class of tumour type found here. They

are often multinodular in nature, each nodule being composed of one particular internationally named histological type of breast cancer separated from the other by a well defined connective tissue band. In their invasive forms, any of the histological types can invade the neighbouring breast tissue either alone or in combination with the other type. Their lymph node metastasis may also contain two histological types of tumour in some cases. They are often associated with fibrocystic disease of the breast, adenosis or mammary duct ectasia. They are found in both female and male breast lesions. There are 7 female and 3 male cases in the series.

Carcinoma of breast with composite histological structure found in both females and males and their actual ages are shown as follows :

1. In 28 year old female:

   Intraductal carcinoma (I, B. 1) and carcinoma with diffuse fibrosis (I, B. 3) in combination with circumscribed carcinoma (I, B. 4).

2. In 33 year old female:

   Intracystic carcinoma (I, B. 2), and carcinoma with diffuse fibrosis (I, B. 3) in combination with circumscribed carcinoma (I, B. 4).

3. In 33 year old female:

   Carcinoma with diffuse fibrosis (I, B. 3) in combination with medullary carcinoma (I, B. 7).

4. In 50 year old female:

   Intraductal carcinoma (I, B. 1) and carcinoma with diffuse fibrosis (I, B. 3) in combination with circumscribed carcinoma (I, B. 4).

5. In 50 year old female:

   Intraductal carcinoma (I, B. 1) in combination with circumscribed carcinoma (I, B. 4).

6. In 50-year old female:

   Intraductal carcinoma (I, B. 1) and invasive papillary carcinoma (I, B. 5) in combination with medullary carcinoma (I, B. 7).

7. In 80-year old female:

   Intraductal carcinoma (I, B. 1) in combination with breast carcinoma with sarcomatoid metaplasia (I, B. 10).

8. In 50-year old male:

   Invasive lobular carcinoma (I, A. 2) and carcinoma with diffuse fibrosis (I, B. 3) in combination with circumscribed carcinoma (I, B. 4).

9. In 60-year old male:

Intraductal carcinoma (I, B. 1) and carcinoma with diffuse fibrosis (I, B. 3) in combination with circumscribed carcinoma (I, B. 4).

10. In 62-year old male:

Carcinoma with diffuse fibrosis (I, B. 3) and invasive papillary carcinoma (I, B. 5) in combination with circumscribed carcinoma (I, B. 4).

The histological type of breast carcinoma most commonly found in combination with one or two other histological types in this series is intraductal carcinoma (I, B. 1) composed usually of intraductal solid, comedo, cribriform or intraductal papillary carcinoma in various combinations. Intraductal carcinoma, usually of multicentric origin, is often associated with fibrocystic disease of the breast. It occurs in all ages starting from the third decade of life, onwards and accounts for about 13 per cent of all histological types of carcinoma found here. All the carcinomas with composite histological structures are neoplasms of mammary tissue proper, and are of ductal epithelial origin, except the single case observed in a 50-year old male patient who had invasive lobular carcinoma (I, A. 2), which is a neoplasm of lobular epithelial origin, in combination

with carcinoma with diffuse fibrosis (I, B. 3) and medullary carcinoma (I, B. 7), which are neoplasms of ductal epithelial origin.

Carcinoma with combined histological structures may sometimes be histologically confused with circumscribed carcinoma which usually, is not only multicentric but also may form glandular and papillary structures. But the average age of females with former lesion is 46 years compared with 44. 3 years for the patients with the latter. In the male only one case of circumscribed carcinoma was diagnosed in a man aged 48 years, and distinction of this type of lesion from carcinoma with composite histological structures in the male may not present any problem. It seems that, on the whole, in Nigeria carcinoma of breast with composite histological structures afflicts older patients in both sexes than most of the other common histological types of breast carcinoma.

In conclusion, there is no doubt that medullary carcinoma with polymorpho-nuclear leucocytic infiltration and carcinoma of breast with composite histological structures do exist in Nigeria and perhaps, in other parts of tropical and temperate zones of the world. Their international recognition, nomenclature and their inclusion under the (sub-group I, B) of the internationally classified groups of breast cancer is highly desirable, in order to avoid difficulties that

may arise in typing various histological types of breast cancer that may be encountered in the tropical Africa (Nigeria).

Geographical epidemiology of histopathology of breast cancer:

In order to establish the avenue for geographical histopathology some of the histological types of breast cancer found in Nigeria are compared with those found in Boston and Tokyo by MacMahon, Morrison, Ackerman, Lattes, Taylor and Yuasa (1973) in table XL which shows the percentage distribution of some invasive histological types of breast carcinoma seen in these three nations.

TABLE XL

Percentage Distribution of Some Histological Types of Breast Carcinoma in Nigeria, America and Japan

Histological Type	Nigeria (240 cases) %	(MacMahon et al) Boston (100 cases) %	Tokyo (100 cases) %
Medullary carcinoma	26	1.4	8.8
Colloid carcinoma	4	2.6	4.2
Small cell lobular ca.	5	7.8	1.0
Papillary carcinoma	9	0.0	0.1
Ductal carcinoma	26	84.4	79.1

Medullary carcinoma as shown in this table is more frequent among Nigerian and Japanese women than among American women (white). Ductal carcinoma, (intraductal and carcinoma with diffuse fibrosis), is far more frequent in both American and Japanese than in Nigerian female patients. Colloid carcinoma is commoner in the Japanese women than in both Nigerian and American women. Lobular carcinoma, on the other hand, is more frequent among American female patients, than among Nigerian and Japanese female patients. Papillary carcinoma appears to be frequent among the Nigerian female patients than among Japanese and American female patients. Wynder, Kajitani, Kuno, Lucas, De Palo and Farrow (1963) compared the distribution of histological types of tumours in American and Japanese patients and had earlier come to the conclusion that intraductal, medullary, and colloid carcinomas are more frequent among the Japanese than among the American patients. Berg and Robbins (1969) from the Memorial Hospital, America, had shown that medullary, and colloid carcinomas are also proportionately more frequent in the American black than in the white American patients, while lobular carcinoma is more frequent in the latter than in the former.

There is racial and geographical differences in the incidence rate of breast carcinoma in general, Doll, Muir and Waterhouse (1970).

It occurs more in the American white nations than in the Japanese, American blacks and in Nigerians. The present histological survey has also revealed that there is a definite racial and geographical difference in distribution of histological types of breast carcinoma. While lobular carcinoma appears to be more frequent in American white women, medullary carcinoma and colloid carcinoma appear to be proportionately more frequant in Japanese women , American black and Nigerian women.

It is a fact that Nigerian and Japanese women are of different races, have different colour of skin, and live in different geographical areas of the world. In spite of these facts, they have been shown in this thesis to share the following in common :

(1) Most Nigerian and most Japanese women have been shown to breast feed their children, while most European and American women nurse their children with variants of cows milk.

(2) Nigerian and Japanese women have been shown to have a lower incidence rate of breast carcinoma than most Europeans and Americans.

(3) Nigerian and Japanese women have been shown to have a higher incidence of medullary carcinoma than white American women.

Host resistance to cancer is chiefly mediated by the cellular immune system, namely competent lymphocytes. The degree of host immune response to tumour varies from individual to individual and from race to race. Nigerian women with breast carcinoma, and Japanese women with the same disease (Wynder, Bross, Kajitani, Kuno, Lucas, De Palo and Farrow (1963)) tend to have a noteable lymphocytic response to their overt carcinoma than white American women with breast carcinoma.

Medullary carcinoma, which is commoner in Nigeria and Japan than America, is a histological type of breast carcinoma considered to have a better prognosis than the common forms of infiltrating duct carcinoma, Moore and Foote (1949), Richardson (1956), McDivitt, Stewart and Berg (1968), and it is, histologically, identified by its accompanying lympho/plasma cells. The hypothesis being tendered for all these observed similarities between Nigeria and Japan, and the difference between these two nations and America is as follows :

(a) Breast feeding involves milking by massaging the breast.

(b) Massaging the breast apart from causing trauma to delicate secretory mammary glands of lactation, may cause escape of products of desquamated mammary ductal epithelial cells into the general circulation.

(c) These products may then be taken up by the reticulo-endothelial cells which may harness them to produce cell-bound antibodies in the competent lymphocytes. The lymphocytes storing these antibodies are referred to as "memory cells".

(d) When any transformational stimuli, which may possibly be a carcinogenic milk factor, akin to Bittner milk factor, which may be common in both Nigerian and Japanese females, transform sensitised ductal epithelial cells into incipient carcinoma (e.g. medullary carcinoma), the host memory cells (sensitised lymphocytes) are released in abundance into the circulation to invade the carcinoma.

It may then be possible to postulate that in both Nigerian and Japanese women, all the epithelial cells of the mammary glands may be sensitised during lactation. Transformation of sensitised ductal epithelial cells into incipient carcinoma by a possible carcinogenic milk factor probably akin to Bittner milk factor may invoke massive infiltration of the cancer by immune lymphocytes, (memory cells). This may explain why noteable lymphocytic response to overt carcinoma is observed more in Nigerian and Japanese women, who naturally breast feed their children, than in most white American women, who

artificially nurse their children.

It may also be that the reason why medullary carcinoma is more frequent in the nations that breast feed their children (Nigeria and Japan), than in the nations, that do artificially feed their children (America) is that a specific milk factor probably akin to Bittner milk factor (1936), common to both Nigerian and Japanese women, may specifically induce development of medullary carcinoma more frequently in the former group of women than in the latter, group of women. In order words medullary carcinoma may be more influenced by common aetiological factors operating in Nigeria and Japan than by those operating in America.

Comparison of male and female breast carcinomas.

Breast carcinomas occur more in the left side in the males than in the right, and more in the right side in the females than in the left. Nigerian men tend to develop breast carcinoma at much older age than Nigerian women. There is no difference between the main histological types of breast carcinoma found in the male breast lesions and those found in the female lesions. While medullary carcinoma is the most common histological type of female breast carcinomas, papillary carcinoma is the main histological type of male breast carcinoma. Norris and Taylor (1969), showed that in American men, infiltrating

duct carcinoma is the commonest histological type in the American males with breast carcinoma, while papillary carcinoma is the second commonest. Haagensen (1971) found also that intraductal carcinoma is commoner than papillary carcinoma among his male breast carcinomas. Table XLI, compares the histological types of male breast carcinoma obtained in Nigeria with those obtained in American males by Norris and Taylor (1969), and by Haagensen (1971).

TABLE XLI

Histological Types of Male Breast Carcinoma Obtained In Nigerian Males Compared with those Obtained In - American Males

Histological Type	Nigeria No. of cases	America Norris et al (1969) No. of cases	America Haagensen (1971) No. of cases
Papillary carcinoma	9	9	7
Infiltrating duct carcinoma	1	84	-
Intraductal carcinoma	3	8	11
Mucoid carcinoma	1	1	1
Paget's carcinoma	1	-	1
Small cell ca. (lobular carcinoma)	3	-	1
Apocrine carcinoma	-	-	1
Circumscribed carcinoma	1	-	-
Well differenciated ca. (Grade I)	-	1	5
Moderately differentiated carcinoma (Grade II)	-	-	5
Undifferentiated ca. (Grade III)	-	-	15
Non-specific adenocarcinoma	-	7	-
TOTAL :-	19	113	47

Though the histological classifications varies from author to author, it is apprent that there is not much difference between the male histological types of breast carcinoma found in both American and Nigerian men; while carcinoma with diffuse fibrosis and intraductal carcinoma are commoner in the Americans, papillary carcinoma is commoner in Nigeria. Lobular carcinoma invasive, which is commoner in the American white women than in Nigerian women, is commoner in Nigerian males than in American males. Haagensen (1971) saw only one such case in his series, while Norris and Taylor (1969) did not report any such case at all, and in Great Britain (Scotland) Sandison (1962) found that majority of male cancers was infiltrating duct carcinoma, but all types, except lobular carcinoma, were noted.

International comparison of age-distribution of various histological Types:

It is apparent that age and breast cancer type are definitely related in all races. Thus Burkitt's lymphoma of the breast and reticulum cell sarcomas are malignant tumours of reticulo-endothelial system most commonly afflicting the breast of the young patients in Nigeria. Lymphosarcomas are also diseases that predominantly affect the breast of both young female and male Nigerians. These diseases are rarely seen after the menopause in women. A similar observation was made by McClanahan and Hogg (1954) in American women, where they observed that among breast sarcomas, angiosarcoma, but not

Burkitt's lymphoma as seen in Nigeria, is a disease of the young women. Carcinomas are the diseases of the older females and male patients. Breast carcinoma occur at older age in men than in women. While the youngest female patient with breast carcinoma in the series is 16 years of age, the youngest male is 31 years of age.

The most common carcinoma in premenopausal women here are carcinoma with diffuse fibrosis, and medullary carcinoma while circumscribed carcinoma is the disease of older premenopausal women (30-39 years of age). Papillary carcinoma, Paget's disease of nipple, lobular carcinoma and colloid carcinoma are definitely diseases of menopausal and post-menopausal women. Medullary carcinoma, the commonest of all histological types of breast carcinoma locally and carcinoma with diffuse fibrosis occur in all age groups. The two elderly, 80-year old females in the series had medullary carcinoma. There is a difference of 2.8 years between the average ages of patients with lobular carcinoma, and medullary carcinoma and of 5.3 years between those with colloid carcinoma and medullary carcinoma. Internationally, the average and median ages of patients with various types of breast carcinoma obtained in Nigeria is compared with those obtained for American females by Berg and Robbins (1959).

TABLE XLII

International Comparison Of Average Ages Of Various Histological Types

Histological Types	Average Age Nigeria (current)	Average Age America Berg and Robbins(1959)
Medullary carcinoma	42.7	50.6
Invasive lobular carcinoma	45.5	52.1
Infiltrating duct carcinoma	43	53.0
Paget's disease of nipple	44	54.0
Papillary carcinoma	42.1	55.1
Colloid carcinoma	48	55.8

In both Nigerian and American nations medullary carcinoma tend to occur on the average in younger women, though Nigerian patients tend to be much younger than the American patients. In both nations, colloid carcinoma occurs in much older women with an average age of 48 and 58.8 years respectively, but the American patients are, on the average, 7.8 years older than their Nigerian counterparts. Lobular carcinoma, which is commoner in the American female patients, occur in much older patients in American women than in Nigerians. The difference in average ages between a Nigerian

female with medullary carcinoma, and one with colloid carcinoma is 5.3 years which is comparable with 5.2 years obtained for the difference between the American patients with medullary carcinoma and colloid carcinoma. It is therefore, obvious that average ages hint at realities of age distribution on incidence pattern of breast carcinoma in various nations.

General Microscopic Features:

Malignant tumours all over the world can undergo haemorrhagic, coagulative, and liquefaction necrosis, and the host reaction to the presence of tumours, comprising of lymphocytes, plasma cells, histiocytes, polymorpho-nuclear leucocytes, and eosinophils are equally universally the same. It is however, observed that in Nigeria (current) and in Japan, Wynder, Bross, Kajitani, Kuno, Locas, De Palo and Farrow (1963), the females tend to have a notable lymphocytic response to their overt carcinomas than the white American women with breast carcinomas. Eosinophils are sometimes abundant in some of the tumours seen locally, particularly in some invasive papillary carcinomas. The part they play in presence of cancer is not known, and its needs investigation. The role of polymorpho-nuclear leucocytes as inflammatory host cellular defence mechanism and the lympho/plasma cells as host immune response to the presence of

/breast cancer

has been stressed in page 106 of this thesis. These observations are of prognostic value for it is found that tumours heavily infiltrated by lympho/plasma cells and polymorpho-nuclear leucocytes, may have better prognosis than those with scanty or no lympho/plasma cells. The associated lymph nodes in such cases often show marked hypertrophy due to follucular or parafollicular hyperplasia associated with hyperlasia of the sinusoidal histiocytes.

Microcalculi and Breast Cancer

Patton, Poznanski and Zylak (1966) first called attention to the clinical importance of radiographically demonstrable microcalculi in non-palpable breast cancers. Since then, Rogers and Powell (1972), Rosen, Synder and Robbins (1974), including many other European authors, have stressed on the importance of breast specimen radiography as a form of the Pathologist's armamentarium for the study of mammary lesions (Gallager, 1975). This latter author has stressed that mammography is capable of an accuracy of 87 per cent to 90 per cent in the diagnosis of breast cancer. He has also shown that calcifications in breast cancer are of two types. One of these is due to the necrosis of intraductal non-invasive carcinoma. This appears to be a universal phenomen, for it is observed that microcalculi are found locally in solid and comedo non-invasive intraductal

carcinoma (see fig. 7). Scattered, small microcalculi has also been observed in areas of fibrocystic disease of the breast, and as such in nearly all the histological types of breast carcinoma found associated with fibrocystic disease in Nigeria (see Table XXX, on page 83). Microcalculi are also found in all lobular carcinoma in situ reported here. A case of breast carcinoma with osseous/cartilagenous meta plasia is also observed in the series (see fig.8).

Mammography would appear to have a great clinical value in all the developing parts of Africa as in other parts of the world for diagnosing symptoms referable to the breast. Its value here may be greatly appreciated when it is applied in screening asymptomatic women in urban and rural areas (Mass radiography) for early diagnosis of breast cancer.

Depigmentation Phenomenon:

The process of depigmentation of black skin overlying a large mammary cancer has been stressed. The importance of this finding in Africa is that biopsy taken from a deeply situated breast carcinoma may reveal malignant cells laden with melanin granules. This may lead one who is not aware of this phenomenon to erroneously diagnose malignant melanoma of the breast; for it has been shown in this

current study, that malignant cells are capable of phagocytosing melanin granules (figs. 14 and 15).

Microscopic Vascular Spread of Various Histological Types:

Any of the malignant invasive tumours of the breast seen here may form tumour emboli in the dilated venous or lymphatic channels that may be widely spread in the parenchyma of the affected breast. This is particularly common in inflammatory carcinomas, and most invasive types of carcinoma seen here. When this is observed in a biopsy specimen, the pathologist may confidently suggest radical mastectomy with thorough axillary lymph nodes clearance to the surgeons, for inevitably the neighbouring axillary lymph nodes would have been involved by the cancer. Pathologists all over the world do make use of the assessment of lymph nodes related to a primary tumour as perimeter for establishing the prognosis in a given tumour. The study of the lymph nodes metastases in the current retrospective study has enabled one to assess the aggressiveness of various histological types of breast cancer encountered in Nigeria. The most aggressive tumour in Nigerian females appears to be carcinoma with diffuse fibrosis. This current finding is similar to what obtains in most European and American countries - Haagensen (1971).

Although medullary carcinoma is regarded as a carcinoma with a better prognosis than most intraductal carcinomas by most European and American authors, Moore and Foote (1949), Richardson (1956), McDivitt, Stewart and Berg (1968), in Nigeria it is observed that it is second to carcinoma with diffuse fibrosis (scirrhous carcinoma) as one of the aggressives types of cancer encountered. This may probably be due to the fact that a greater number of medullary carcinoma with neither lympho/plasma cell nor polymorpho-nuclear leucocytic infiltration were included in the calculation. Medullary carcinoma is followed by papillary carcinoma, lobular and intraductal carcinomas as other aggressive types of tumour locally. The colloid carcinoma does not appear to be aggressive, and is least likely to metastasise. In the male, the most aggressive histological type is invasive papillary carcinoma. This is probably due to the fact that it is the commonest histological type of male breast cancer here. Male lobular carcinoma when invasive can be rather aggressive. It appears that the rare carcinoma of breast with apocrine metaplasia can be also rather aggressive in the male.

Some Special Histological Types of Breast Carcinoma

Lobular Carcinoma (Group I, A):

A detailed histological study on lobular carcinoma as one of the special histological types of breast carcinoma has been given in page 54 of this thesis. This is because lobular carcinoma is the only histological type of breast carcinoma of mammary tissue proper originating from mammary lobular epithelial cells, that has been so far described by most European and American authors. Moreover, lobular carcinoma, *in situ* has recently generated much interest in medicine as to whether it is a malignant condition that can progress to invasive form with time. Also, in the interest of geographical pathology it has become necessary to point out that lobular carcinoma occurs in African males more than it occurs in European and American males. Lobular carcinoma has been sub-classified into:

(a) lobular carcinoma *in situ* (Group I, A. I)

and

(b) lobular carcinoma invasive (Group I, A. 2)

It accounts for about 5 per cent of all carcinomas encountered in Nigeria. The ensuing discussion on it lays special emphasis on lobular carcinoma in male breast lesions.

Ewing (1919), in the first edition of his book, "Neoplastic Diseases", had presented a photomicrograph, fig. 184, in his text

book which he described as a precancerous change. He did not give a specific name, but it was obvious that the lesion was lobular carcinoma in situ as was later classically described by Foote and Stewart (1941). Stewart (1950), after extensive study on lobular carcinoma classified it into non-infiltrating and infiltrating types. McDivitt, Hutter, Foote and Stewart (1968), gave sufficient data to show that in situ lobular carcinoma is a pre-invasive form of breast cancer that can progress, in time, to infiltrating lobular carcinoma, which they showed, had a distinctive microscopic appearance. Over the years, a number of case reports on lobular carcinoma have appeared in the European and American literature, Miller and Kay (1956), Haagensen (1962), Warner (1969) and many others. But it was only recently that it took Gad and Azzopardi (1975) to show that both in situ and infiltrating lobular carcinoma are mucin-secreting type of tumours, a modern discovery which is at variance with the view that these tumours are exclusively of myoepithelial-cells, Hamperl (1972). Gad and Azzopardi (1975) stated clearly that lobular carcinoma is a tumour that differentiates towards secretory cells.

All these excellent case reports on lobular carcinoma were written mainly on female breasts as though it is the feminine mystique, Lewison (1964). This may appear to be the case in most European

and American countries for Sandison (1962) had found that in Scotland, the majority of male carcinoma was infiltrating duct carcinoma, but however noted all other histological types, except lobular carcinoma. Holleb, Freeman and Farrow (1968), did not find any lobular carcinoma amongst the types of carcinoma that afflict American male breasts. Berg and Robbins (1969), specifically stated that lobular carcinoma is not seen in the male, and medullary carcinoma is relatively uncommon, while papillary carcinoma is diagnosed more often in men than women. Warner (1969), who wrote an excellent report on lobular carcinoma of the breast, did not include any lobular carcinoma among her male types of breast carcinoma. Haagensen (1971) recently found one case of small cell carcinoma (lobular carcinoma invasive) among the 47 cases of male breast carcinoma in American men he studied, and gave excellent illustrations in his figures 38-8 and 38-9, page 788, in his text book on the histological types of the tumour. He however emphasized that this type of carcinoma has a favourable prognosis. The current African study has however shown that both in situ and infiltrating lobular carcinoma do occur in both Nigerian females and males. It is more frequent in American females than in Nigerian and Japanese females, but appears commoner

in Nigerian males than in American and European males.

Lobular carcinoma, as defined by Warner (1969), is a mammary carcinoma arising in lobules and terminal ducts, the in situ form is confined to their site of origin, while the infiltrative form spreads outside these structures. Most of the in situ lobular carcinoma here are incidental microscopic findings in female breast lesions diagnosed as fibrocystic disease. This finding is not surprising when it is recalled that 37 years ago, Foote and Stewart (1941), stated that such a carcinoma could not be diagnosed clinically but in most cases can only be diagnosed as an incidental microscopic finding in a patient operated on for some other lesions, often fibrocystic disease of the breast. No case of lobular carcinoma in situ was found in association with all the 8 cases of gynaecomastia studied here, and no European literature has yet described any association between gynaecomastia and in situ lobular carcinoma. Although not seen in this series, McDivitt, Stewart and Farrow (1967), reported 13 cases of lobular carcinoma in situ arising within a benign fibro-adenoma, while Goldman and Friedman (1969), reported 3 cases. Haagensen (1971) found typical lobular carcinoma in situ in close association with giant fibroadenoma in 4 of his cases, some being localised entirely within the lesion while in others the lesion was multifocal in origin. All the lobular

carcinoma in situ, and about 67 per cent of all the invasive lobular carcinoma diagnosed here are associated with fibrocystic disease of the breast. One male patient with carcinoma of breast with composite histological structures had invasive lobular carcinoma in combination with carcinoma with diffuse fibrosis and medullary carcinoma and one case has been seen complifated by Paget's disease of the nipple. There is no doubt that in situ lobular carcinoma is pre-invasive and can progress to invasive form, Warner (1969). It is of clinical interest to know that most lobular carcinoma in situ seen here are often associated with microcalculi which is often seen in breast tissue adjacent to the tumour. This is important from early diagnostic point of view using mammography. Most of the invasive forms seen here are usually associated with lobular carcinoma in situ. When the cytological and histological features of an invasive cancer are identical to those of infiltrating cancer seen in association with lobular carcinoma in situ, the diagnosis, infiltrating lobular carcinoma, may be justifiable, without having to identify an intralobular in situ carcinoma (Fechner, 1972). This is highly probable. Acinar/nodular pattern for instance, may be highly suggestive, but not, it is believed invariably diagnostic of

invasive lobular carcinoma. This may be true as the current study has shown that the small malignant cells of invasive lobular carcinoma can variously align themselves into various iden tifiable patterns e.g. Indian file pattern and acinar/nodular pattern which may be either alone or in combination, (figs. 38, 42 and 45) and in some cases they may be arranged in sheets, columns, and nodules (fig. 43a) without any associated in situ lobular carcinoma.

The stated median age of 45 years for American females with this type of tumour (Warner, 1969), is 2 years greater than the median age of 43 years for Nigerian women with the same type of carcinoma. The majority of Nigerian patients are in their 4th decade of life with a range of 26-70 years. These findings are analogues to average age figure of 48.3 years for American women with lobular carcinoma invasive, (Newman, 1963), and to the range of 29 to 83 years quoted for American women by Renfield, Jacobson and Warner (1965), and by McDivitt, Stewart and Farrow (1967). Nigerian women with lobular carcinoma are therefore, about 3 years younger than their caucasian counterparts with the same disease. The average age of Nigerian male patients with lobular carcinoma here is 65 years which is greater than the average age of 52.6 years of Nigerian males with carcinoma in

general. The males with lobular carcinomas invasive here are much older than their female counterpart with the same disease. In general invasive lobular carcinoma is a disease of older females and males in this community.

Occurence:

The frequency of lobular carcinoma in Newman's (1966) series of 1,436 mammary cancers was 10.2 per cent, 5 per cent of these were lobular carcinoma in situ and 5.2 per cent were invasive lobular carcinoma. Warner (1969) out of 285 consecutive malignant tumours she encountered, observed that lobular carcinoma constituted 5.3 per cent of the total, the cases being divided equally between the in situ and infiltrating forms. These American figures are compared with those obtained for Nigerian patients in table below. It is obvious that both types of lobular occur in Africa (Nigeria) and in America with a moderate variation in percentage incidence.

TABLE XLVIII

Frequency of Lobular Carcinoma in Nigeria (Current) America (Newman) and America (Warner)

	NIGERIA (Current)		AMERICA (Newman) (1966)	AMERICA (Warner) (1969)
Number of Cases	(168)*	(420)*	(1,436)	(285)
Lobular carcinoma in situ	4.2%		5%	2.6%
Infiltrating lobular carcinoma.		5%	5.2%	2.65%

(168)* - Number of fibrocystic disease of the breast reviewed.

(420)* - Number of carcinomas reviewed.

Behavoural Pattern:

It has been shown that 17 per cent of invasive lobular carcinoma in the male and 5 per cent in the female have metastasised to the axillary lymph node by the time the diagnosis was made. This tumour appears to be second to papillary carcinoma as the most invasive type of carcinoma in the males, while in the females it is 5th to carcinoma with diffuse fibrosis. The example of behavioural pattern of lobular

carcinoma illustrated in the 60-year old man portrays lobular carcinoma as having rather an aggressive nature once it becomes invasive. Its diffuse invasion, destruction and replacement of the mammary parenchyma, and the readiness with which it has metastasised to the axillary regional lymph nodes, compares very well with the behavioural pattern of carcinoma of the breast with diffuse fibrosis (scirrhous carcinoma). The observed generalised miliary metastases to the serous surfaces of the pleura with massive bilateral serous effusion, mimicks the behavioural pattern of serous adenocarcinoma of the ovary, which, once it breaks through its ovarian capsule, and gains access to the peritoneum, gives rise to massive peritoneal seedlings, carcinomatosis peritonei, which is always associated with intractable ascites. All these observations clearly demonstrate that lobular carcinoma, once invasive has the capacity to metastasize and to kill rapidly as has been illustrated by the 60-year old man, who had only 3 months history of the disease that killed him shortly after his admission. The observation made by Haagensen (1971) that small cell carcinoma (lobular carcinoma invasive) is a type of carcinoma that has a favourable prognosis is not endorsed here. Rather it is concluded with Berg and Robbins (1963), who after analysing cases of breast carcinoma for 20 years concluded that the prognosis of infiltrating

lobular carcinoma is no better than that of infiltrating ductal carcinoma and actually may be worse.

Medullary Carcinoma (Group I, B.7) and Circumscribed Carcinoma (Group I, B.4):

Moore and Foote (1949) first defined medullary carcinoma and regarded it as a histological type of breast carcinoma with a more favourable prognosis than the ordinary infiltrating duct carcinoma. They suggested that the prominent lympho/plasma cell infiltrate, in medullary carcinoma might reflect a "maladjustment between the tumour and the host", and that this phenomenon could be partly responsible for the better prognosis they observed in patients with medullary carcinoma. Richardson (1956), reported on 117 patients with medullary carcinoma and confirmed many of the findings of Moore and Foote (1949). McDivitt, Stewart and Berg (1968); MacMahon, Morrison, Ackerman, Lattes, Taylor and Yuasa (1973), all agreed with the former authors that medullary carcinoma had a good favourable prognosis. Haagensen (1971), however, preferred the name "circumscribed" to medullary carcinoma because of this striking feature. Recently Rodolfi, Rosen, Porta, Kinne and Mike (1977), carried out a detailed study on medullary carcinoma and unlike the other former authors, it became clear to them in the course of their study that they

were faced with a spectrum of tumours. Some of their cases showed all the hallmarks typically ascribed to medullary carcinoma, while others appeared to deviate from this component pattern to varying degrees, some having microglandular and intraductal components. They therefore defined, a typical medullary carcinoma as a tumour with a predominant syncytial growth pattern, completely circumscribed margin, and a moderate to marked diffuse mononuclear stromal infiltrate and without a recognisable intraductal component or areas of microglandular differentiation. On the other hand, they categorised any other tumour with any deviation from these criteria as atypical medullary carcinoma.

The following table XLIV shows the histological criteria Rodolfi and his colleagues laid down for differentiating between typical and atypical medullary carcinoma.

TABLE XLIV

HISTOLOGICAL CRITERIA FOR CLASSIFICATION OF THE CARCINOMAS - RODOLFI et al (1977)

Typical Medullary (All of the following features)	Atypical Medullary (Features of typical medullary but with any of the following)
Predominantly syncytial growth pattern (75 per cent)	Predominantly syncytial growth pattern (75 per cent)
Microscopically completely circumscribed	Areas of tumour margins show focal or prominent infiltration.
No intraductal component	Intraductal component present or prominent
Moderate to marked diffuse mononuclear stromal infiltration	Mild or negligible mononuclear infiltrate or infiltrate margins only
Absence of microglandular features Nuclear grades 1 and 2.	Presence of microglandular features Nuclear grade 3

These authors felt that the tumours they included in the category of atypical medullary caricnoma represent a heterogenous group that should be more appropriately be classified as infiltrating duct carcinoma. They did not believe that there would be any advantage in establishing a separate diagnostic subcategory under the name atypical medullary carcinoma. Rather, by taking their findings into consideration it is possible to determine whether a tumour is

appropriately described as a medullary carcinoma. They went on to say that under these strictly defined circumstances medullary carcinoma proved to be a distinct morphologic entity with a prognosis that was significantly more favourable than that of ordinary infiltrating duct carcinoma. With all these in view, a detailed study of medullary carcinoma (Group I, B. 7) and circumscribed carcinoma (Group I, B.4) has been carried out in this current study to provide evidence for establishing a separate diagnostic criteria to categorise atypical medullary carcinoma of Rodolfi and his colleagues (1977), and justify its nomenclature as circumscribed carcinoma and its classification as belonging to neoplasms of mammary tissue proper (Group I) and its subsequent sub-classification among the neoplasms of ductal epithelial origin, by the Pathology Working Group, Breast Cancer Task Force, National Cancer Institute of America (1973) - see pages 94-115.

Medullary carcinoma and circumscribed carcinoma are among the 8 common histological types of breast carcinoma encountered in Nigeria, the former being commoner than the latter. Both tumours belong to neoplasms of mammary tissue proper (Group I) and sub-grouped rightly under neoplasms of ductal epithelial origin, and labelled as circumscribed carcinoma (Group I, B.4) and medullary carcinoma (Group I, B.7).

Sex Distribution:

All the 116 cases (26 per cent) of medullary carcinoma diagnosed were from female breast lesions, and none was discovered in the male. Morris and Taylor (1969) and Haagensen (1971) equally did not include medullary carcinoma among their list of various histological types of male breast carcinomas. On the other hand, circumscribed carcinoma, occurred in both female and male breast lesions in the present series. In the female it accounted for 12 per cent (52 cases) of all the female carcinomas. Although only one case was diagnosed in the male, it was commonly found in carcinoma with composite histological features in both male and female breast lesions. Both lesions have been described in pregnant and lactating women, and have both given rise to inflammatory carcinoma in some women.

Age Distribution:

The percentage age distribution of both medullary and circumscribed carcinomas respectively is shown in table XLV.

TABLE XLV

Percentage Age Distribution of the Two Case-Types

	(10)16-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89
Medullary carcinoma	0	9	23	34	22	11	0	2
Circumscribed carcinoma	0	0	22	42	22	11	3	0

The youngest female patient with medullary carcinoma in this series is aged 20 years, and the oldest is 80 years of age; while on the other hand the youngest female patient with circumscribed carcinoma is 30 years of age, and the oldest is 70 years of age. It is obvious that medullary carcinoma begins to afflict female breasts in much earlier age-groups than circumscribed carcinoma. It is to be noted from the table that both types of tumour are equally commoner in the pre-menopausal and menopausal, than in the post-menopausal females. Rodolfi and his colleagues (1977), observed that only one-third of the patients with typical medullary carcinoma were premenopausal, while those with atypical medullary carcinoma were intermediate in menopausal group. They suggested that the difference in menopausal status between the groups of tumour was significant.

The current author agrees with this finding.

Average Age:

Table XLVI shows the average ages of both medullary carcinoma and circumscribed carcinoma respectively.

TABLE XLVI

AVERAGE AGE OF TWO CASE-TYPES

Histological Type	Average age	Median age	Modal age
Medullary carcinoma	42.7	43	45.5 (41-50)
Circumscribed ca.	44.3	43.8	43 (41-50)

It is obvious that patients with circumstribed carcinoma are on the average older than patients with medullary carcinoma, although their modal ages are approximately the same. Rodolfi and his group (1977) on the other hand, found that the average age of these patients with typical medullary carcinoma is 52 years compared with 51 years for the patients with atypical medullary carcinoma. The American patients in both instances are on the average much older than the Nigerian patients.

Pathological Features:

Both medullary and circumscribed carcinomas encountered here are usually bulky and well circumscribed tumours that often cause depigmentation of the overlying skin. They both may fungate and

ulcerate through the skin, to become secondarily infected as illustrated in photograph 2. Their cut surfaces are often well circumscribed, and bulging above the level of the surrounding breast tissue. The cut surface of circumscribed carcinoma is usually markedly lobulated as shown in photographs 6, 7 and 9. Both tumours are liable to haemorrhage, coagulative, liquefaction necrosis and cystic degenerative changes (photograph 8).

Microscopic Features:

Necrotic areas in both cases can be associated with micro-calculi. Medullary carcinoma and circumscribed carcinoma may respectively be the underlying mammary carcinoma, associated with a given case of Paget's disease of the nipple (photographs 93 and 102). Twenty-seven (27) per cent of medullary carcinoma, and 19 per cent of the circumscribed carcinoma are respectively associated with fibrocystic disease of the breast.

Microscopic Metastases:

Both tumours do give rise to axillary lymph nodes metastases. Twenty-two (22) per cent of the medullary carcinoma studied had histologically proven axillary lymph node metastases; while in the circumscribed carcinoma it is 18 per cent. The higher percentage observed in medullary carcinoma may be due to the fact that a higher

number of medullary carcinoma with no lympho/plasma cell infiltration were diagnosed in the series than circumscribed carcinoma. Rodolfi and his colleagues (1977) found no apparent difference in the anotomical sites of metastases among the typical and atypical medullary carcinomas they studied. They did find however, that tumour emboli in lymphatic spaces were noted at the margins of five atypical medullary (circumscribed) carcinoma they studied. They indeed originally excluded tumours with lymphatic emboli from the typical medullary group and their results confirmed lymphatic tumour emboli as an unfavourable prognostic feature. Circumscribed carcinoma, seen here often give rise to metastic tumour emboli in the dilated lymphatic spaces of the affected breast parenchyma (see fig. 18).

Evolution of Medullary and Circumscribed Carcinoma:

It is constantly observed in most of the cases here that both histological types may appear to evolve from areas of adenosis in mammary lobules. Adenosis may occur as the main lesion of the breast by itself but in most cases, it is one of the complex ductular and intraductal epithelial proliferations seen in fibrocystic disease. Adenosis is multicentric in origin. It is a condition where several lobules in a sector of breast are involved, at the same time, in the hyperplastic changes of the lobular ductules and ducts. Figure 117,

shows a low power view of such an area of adenosis in fibrocystic disease. Hyperplastic, cystically dilated ductules and ducts, dispersed in a fibrous stroma, moderately infiltrated by lympho/plasma cells, are seen in several mammary lobules. The lobules are well circumscribed and demarcated by well organised connective tissue which is also sparsely infiltrated by lympocytes and plasma cells. Where an area of adenosis is mapped out as a field for malignant change, the hyperplastic epithelial cells of the proliferating ductules and ducts become dysplastic. The stroma of the lobules become increasingly infiltrated by lympho/plasma cells, (fig. 118). Here, the well circumscribed lobular architectures of two adjacent mammary lobules, are seen being disrupted by infiltrating lympho/plasma cells. The proliferating, dysplastic, ductules and ducts, having increased in number, emerge beyond the border of the disrupted lobules, spreading in the inter-lobular connective tissue around a centrally placed inter-lobular duct. Figure 119 is a high magnification of an area of such disorganised, proliferating, and dysplastic ductules and ducts. As the epithelial cells become malignant in such lobules, massive infiltration by lymphocytes and plasma cells soon become evident. These cells stream along the fibrous stroma and haphazardly separate groups of malignant ductules and ducts into well defined clusters, as portrayed

in the left hand corner of figure 120. Bizarre mitosis and cellular pleomorphism soon become abundant. The lumina of the ductules and the ducts soon become obliterated by the proliferating malignant cells (see fig. 121), which shows aggregates of lymphocytes and plasma cells demarcating sheets of malignant cells - satellite medullary carcinoma. The proliferation of the latter may be so rapid that soon broad continuous sheet of cells, almost syncytial in nature and interspersed by lymphocytes and plasma cells, is formed. Thus in a sector of breast that has undergone such a malignant change, involving several lobules, two things can happen : (a) the adjacent malignant lobules may coalesce to form a large syncytial tumour mass of typical medullary carcinoma. Figure 121 showes two such adjacent malignant lobules beginning to coalesce to form a large syncytial type of medullary carcinoma as seen in lower diagonal corner of the figure, and figure 49 . shows the central area of such a tumour; (b) the adjacent malignant lobules may remain distinct and be completely surrounded by fibrous connective tissue which is heavily or moderately infiltrated by lympho-plasma cells, thus forming the circumscribed carcinoma. Since the latter is a tumour with multilobular pattern, various malignant lobules constituting it, may present composite histological structures. Thus in circumscribed carcinoma the malignant

cells of a lobule may differentiate to form tubular, papillary or microglandular structures, while the adjoining lobules may retain the original medullary pattern as shown in figures 70, 72, 76, and 77. It is apparent that a small biopsy taken from a lobule of circumscibred carcinoma consisting mainly of syncytial medullary components may not be confidently differentiated from typical medullary carcinoma, unless large multiple sections of the lesion are carefully studied. This observation on evolution of typical medullary carcinoma, and circumscribed carcinoma (atypical medullary carcinoma) is similar to that made by Ridolfi and his colleagues (1977) when they wrote: "In the course of the review, we observed extension of the medullary carcinoma cells into ducts and lobules in a substantial proportion of the lesion. Often, this was accompanied by the same prominent mononuclear infiltration that occurred in the main tumour. Study of many such areas suggested that proliferation of the cells within lobular ducts and acini could lead to progressive distention and ultimately to confluence of these structures producing the appearance of a small satellite medullary carcinoma. Table XLVII shows the current histological criteria for differentiating between typical medullary carcinoma and circumscribed carcinoma.

TABLE XLVII

HISTOLOGICAL CRITERIA FOR DIFFERENTIATING THE TWO CASE-TYPES

	Typical Medullary Carcinoma	Circumscribed Carcinoma
1.	Not Multilobular	Multilobular
2.	Completely circumscribed without infiltrating border	Circumscribed with infiltrating border
3.	Predominantly syncytial growth pattern	Syncytial growth pattern sometimes
4.	Epithelial component does not form structure or glands	Epithelial component forms structures and glands
5.	Lympho/plasma cells intimately interspersed among tumour cells centrally	Lympho/plasma cells situated in periphery of tumour mass, and not intimately interspersed among tumour cells centrally
6.	Replacement fibrosis secondarily formed in tumour centre	Central fibrosis formed primarily from mammary fibrous stroma.
7.	Scarring central and minimal and always enclosed by sheets of tumour.	Scarring massive or moderate, and always enclosing sheets or large nests of tumour cells centrally.

These current histological criteria for diagnosing medullary carcinoma and circumscribed carcinoma respectively, are similar to the ones laid down by Ridolfi and his colleagues for differentiating between typical and atypical medullary carcinomas. The above account has shown that clinically, medullary carcinoma can not be differentiated

from circumscribed carcinoma, and the same statement applies to macroscopic features of amputated breast lesions. The similarity between the two, as regards microcalculi formation, association with fibrocystic disease, Paget's disease and lymph node metastases has been stressed. The sex differences in their distribution has been pointed out. While medullary carcinoma begins to afflict female breasts from the third decade of life, circumscribed carcinoma begins at fourth decade of life. Both are, of course, predominantly lesions of the pre-menopausal and menopausal women than of post-menopausal women; circumscribed carcinoma being commoner than medullary carcinoma in the menopausal women. The two types of tumours appear to have identical evolution from mammary ductal epithelial cells. But it appears that during the process of evolution, the malignant cells that compose medullary carcinoma in various malignant lobules, maintain their primitive state, and continue to rapidly proliferate to such an extent that the neighbouring malignant lobules do coalesce to form large syncytial mass of typical medullary carcinoma. Malignant cells of circumscribed carcinoma on the other hand, appear to exhibit some degree of maturation in some malignant lobules where the cells differentiate to form microglandular components, tubules and papillary structures, while the malignant cells of the other lobules may remain

primitive and continue to proliferate and expand to form a satellite syncytial mass that cannot histologically be differentiated from typical medullary syncytial carcinoma, though the former lobules are often well surrounded by connective tissue.

The histological criteria laid down for the two case-types is distinct for the two cases. The ones for diagnosing circumscribed carcinoma is distinct enough to show that circumscribed carcinoma is a distinct morphological entity, with its distinct histological features and perhaps, distinct biological behaviour, that enables the author, unlike Ridolfi and his colleagues, to believe that there is advantage in establishing a separate sub-classification of "atypical medullary carcinoma" under the name circumscribed carcinoma as classified by the Pathology Working Group, Breast Cancer Task Force, National Cancer Institute of America (1973).

Paget's Disease Of Nipple:

The author strongly believes that Paget's cells seen in the epidermis in Paget's disease of nipple are metastatic malignant cells arising from the primary underlying intra-mammary carcinoma for the following reasons :

(1) It is observed in advanced Paget's disease, that Paget's cells are increased in number, compressing

the epidermal squamous cells to such an extent that the squamous cells are thrown into various elongated shapes, forming a net-work, the meshes of which are filled with Paget's cells lying singly or in groups, (figs. 95 and 96).

(2) It is often observed that the basal cells lying between Paget's cells and the underlying dermis are often flattened, (fig. 97).

(3) All the cases of Paget's disease in the series are associated with underlying intra-mammary carcinoma, (figs. 99, 100, 102 and 103).

(4) In some cases the underlying mammary carcinoma may be composed mainly of Paget's cells.

The current view are in agreement with those expressed by Muir (1939), who had earlier made it clear that Paget's disease is a rare complication of intraductal carcinoma which may originate in any part of the duct system, and may arise in multiple independent foci. Inglis, (1946), later confirmed Muir's observations that Paget's cells present in the epidermis are ductal, and not epidermal cells.

In spite of these facts some European and American authors are still doubting the intra-mammary ductal epithelial origin of Paget's cells seen in Paget's disease of the nipple. For instance, the Pathology Working Group, Breast CancerTask Force, National Cancer Institute of America (1973), in their recently modified classification of breast cancer, has still sub-classified Paget's disease of nipple as a neoplasm of undertermined epithelial origin. It is therefore important here to reinstate the observation made forty years ago by Muir (1939) in Scotland, that "intraduct carcinoma of Paget's carcinoma is fundamentally not different from other breast duct carcinomas. It may originate in any part of duct system and may arise in multiple independent foci. If it develops first in the ducts of the nipple it may spread to the nipple epidermis and produce Paget's erosion. If it develops in the ducts in the breast proper it may grow upward in the duct system to reach the nipple." Muir (1939), strongly believes that Paget type of carcinoma is indeed merely "a rare complication of a quite common condition", i.e. intraductal carcinoma. These observations of Muir is still upheld to be right up-to-date and quite recently, Haagensen (1971), had reported that he had not seen an example of Paget's carcinoma of the nipple in which intraductal carcinoma is not found in the duct system of the nipple or breast substance, an observation

well supported by the current study.

Finally, it is important to observe that in Nigeria Paget's cells have a tendency to accumulate melanin granules in their cytoplasm - (Figure 96). Where there is exessive accumulation of melanin granules, the epidermal lesion may closely resemble intra-epidermal malignant melanoma from which it must be differentiated. Fisher and Beyer (1959), and Helwig and Graham (1963), had respectively shown that in Paget's cells the periodic acid schiff (P.A.S.) reaction is strongly positive and diastase resistant, whereas in malignant melanoma this reaction is either negative or only very slightly positive.

Malignant Breast Neoplasm in Pregnancy and Laction in Nigeria:

Towards the end of the last century several surgeons of great experience had noted the exceptional malignancy of breast evolving during pregnancy and had then coined the term "Mastitis Carcinomata". Schumann (1911), gave a detailed description of a case of acute carcinoma mistaken as an abscess in a lactating breast. Lee and Tannenbaun (1924), and Taylor and Meltzer (1938) respectively defined the clinical picture of inflammatory carcinoma which is the modern term for "mastitis carcinomata". Among the presenting symptoms in his series of 89 patients with inflammatory carcinoma, Haagensen

(1971), included :

(a) pain in breast or nipple,

(b) enlargement of breast,

(c) redness of skin,

(d) increased warmth of the skin, and

(e) oedema of skin.

The symptoms and signs presented by the patients in the current study are similar to these. The essential clinical characteristics presented in the current study namely, enlargement and generalised induration of the skin over it are similar to those seen in inflammatory carcinoma. Leucocytosis is often marked as seen in the 5 cases reported by Durodola (1976). Taylor and Meltzer (1938) in their series of 38 cases found that only 5 patients with inflammatory carcinoma had leucocytosis. Burkitt (1958) first described sarcoma involving the jaws in African children, which now bears his name, Burkitt's lymphoma, but he did not describe primary mammary Burkitt's lymphoma. Durodola (1976) was the first Nigerian to report the clinical presentations and management of 5 patients with primary Burkitt's lymphoma of breast presenting during lactation. Bannermann (1966) had earlier reported a case of Burkitt's tumour in pregnancy. Shepherd and Wright (1967) reported 6 patients with Burkitt's tumour presenting as bilateral swelling of the breast in women of child-bearing age and Finkle and

Goldman (1974) recently reported a case of Burkitt's lymphoma in a young pregnant American woman they studied.

While the clinical features of inflammatory carcinoma is universally and internationally the same in most patients, the histological characteristics of the lesions seen in Nigeria appears to differ from those reported by most European and American authors. Thus Taylor, and Meltzer (1938), Meyer, Dockerty and Harrington (1948) and Chris (1950) in their respective studies reported that inflammatory carcinoma is not a special microscopic type, and that all the usual microscopic types of breast carcinoma are found. Haagensen (1971), listed intraductal, circumscribed, scirrhous, small cell and large cell carcinomas as the main histological types found in various inflammatory carcinomas he studied. Of the 59 tumours he microscopically studied adequately, he found that one was well differentiated, 11 were moderately differentiated, and classified 47 cases as undifferentiated. The present study has shown that the malignant neoplasm of reticulo-endothelial origin, particularly, Burkitt's lymphoma and reticulum cell sarcoma, are the main histological types of malignant breast lesions encountered in Nigerian lactating and pregnant women. The histology of reticulum cell sarcoma depicted in this series resembles the inflammatory carcinoma of large cell type which Haagensen (1971) illustrated in

figs. 31-2, page 580 of his text book. In fact it is often difficult to differentiate this type of tumour from medullary carcinoma with no lympho/plasma cell infiltrate, so commonly found in Nigerian women of this age group. Essentially of course, is the clinical management of malignant neoplasia in pregnancy and lactation. Prompt diagnosis of Burkitt's lymphoma by smears stained with Romanwsky stains, will enhance its correct diagnosis, and prompt adequate treatment with cytotoxic agents. It should be emphasized that in countries where Burkitt's lymphoma is endemic, clinicians should be alerted to the possibility of the disease occurring during pregnancy and lactation even in the absence of the usual jaw or abdominal tumours.

(b) SUMMARY

The 12,455 types of cancer recorded during the sixteen year period of this study consisted of 6,418 female and 6,037 male cases. Statistical analysis showed a significant difference in the sex distribution of the cases, with higher proportion occuring in females. They included 6,890 carcinomas with a relative ratio frequency of 54 per cent and 3,015 sarcomas with a relative ratio frequency of 24 per cent. Cancer therefore occurs in Nigeria as elsewhere in the world, carcinomas being commoner than sarcomas. Cervical carcinoma is the commonest type of carcinoma and Burkitt's lymphoma, the commonest type of lymphomas encountered locally.

1,102 female and 43 male breast lesions recorded during this period, consisted of infective diseases, non-infective lesion - fat necrosis, fibrocystic disease, duct ectasis and gynaecomastia; benign tumours - fibroadenoma and giant fibroadenoma; malignant tumours - carcinomas, malignant lymphomas and sarcomas.

Comparison of the current findings with those reported for Great Britain, West Indies and Uganda, showed that breast lesions are common human diseases that have a tendency to show geographical difference in their distribution pattern; carcinomas are commoner causes of breast diseases than benign lesions in Africa, while in Great

Britain and West Indies benign lesions are commoner causes than carcinomas. Female breast lesions occur more in the left than in the right side in the latter nations, and more in the right than in the left side in Nigeria. In all nations male lesions occur more in the left than in the right side.

The recorded 725 cases of breast cancer has a relative ratio frequency of 6 per cent and an average annual incidence of 38 cases. The average age of breast cancer female, is 43 years and that of the males, 53 years. In Ibadan female population of 26,900, 244 women had breast cancer, and in the male population of 35,800, only 3 men had. The calculated annual incidence of breast cancer per 100,000 of Ibadan female population is 5.8 for all ages, and that of male population is 0.04 for all ages. Comparison of the current figures with those compilèd by Doll, Muir and Waterhouse (1970) for other parts of Africa, Asia, India, West Indies, Europe and America led to the following conclusion : 'Breast cancer has a higher incidence rate in the white than in the coloured races. Its incidence is higher in the black Americans and West Indians, whose ancestors had migrated from Africa to their present environment, than in the African indigens, and it is less in Natal Indians than in Indian indigens. It has a ten-fold incidence rate in the peoples resident in temperate zones, than in those resident in

the tropics. Because the incidence rate of, and susceptibility to, breast cancer, appear to be influenced by skin colour, affluency and degree of industrialisation of different nations, the latter have been accordingly grouped into : High risk-group of nations, Great Britain, America (white), South Africa (white), Denmark: Intermediate risk-group of nations, America (black), West Indies, Hungary, Poland: Low risk-group of nations, Nigeria, Rhodesia (black), Natal (indians), India.

The result of comparative epidemiological study on 200 breast cancer female patients and 200 controls has shown that marital status may have no part to play in the aetiology of breast cancer locally, although this may be considered important in caucasians. Diet, social customs and type of occupation may harness other aetiological factors in breast cancer development. Pregnancy, fertility, emotional upset induced in women by death of their children in puerperium, stillbirth and miscarriages, may render the affected women more susceptible to breast cancer. Oestrogenic hormone may play a prominent role in the aetiology of human breast cancer, and may be solely responsible for the higher breast cancer incidence observed in females than in males. Breast feeding may protect women in each ethnic group against developing breast cancer.

It is hypothesised that melanin pigmentation may protect the coloured races against developing as much breast cancer as the white races. Histological study of the available slides on 420 female and 17 male cancers has shown that breast cancer is not just a single disease, but a group of diseases affecting one organ, the breast. It is composed of different histological types of cancer, each with its own peculiar histological features and histological behavioural pattern that helps its identity.

There is no observed racial or geographical difference in the cellular structures of breast cancer, nor in the host cellular reaction to their presence. The sub-classification of medullary carcinoma is based on whether it is accompanied by lympho/plasma cells or not. In Nigeria, apart from lympho/plasma cells, some histological types of medullary carcinoma are constantly accompanied mainly by polymorpho-nuclear leucocytes. This type of medullary carcinoma has been currently named "medullary carcinoma with polymorpho-nuclear leucocytic infiltrate". Another histological type of breast cancer occasionally found locally is one with composite histological structures. This type has been currently named "carcinoma of breast with composite histological structures". It is recommended that these two histological types of breast cancer be recognised and subclassified under groups of neoplasia of ductal epithelial origin.

Papillary carcinoma is described developing in a gynaecomastia, but there is still debate on this type of finding. Fibrocystic disease has a pre-malignant potentiality, but this is still debatable.

Age and breast cancer are definitely related. Locally, Burkitt's lymphoma is a disease of the young, medullary carcinoma that of pre-menopause, while lobular and colloid carcinomas are mainly those of menopause and post-menopause. Medullary carcinoma is commoner in Nigerian, black American and Japanese, than in white American, females. Male lobular carcinoma is commoner in Nigeria than in Europe. Malignant cells and Paget's cells metastatic to black epidermis have ability to phagocytose melanin granules. Under such conditions, they may mimick intraepidermal melanoma from which they must be differentiated. Burkitt's lymphoma is perhaps, a unique tropical disease that appears to afflict female breast in pregnancy and lactation. This may commonly occur in countries where Burkitt's lymphoma is endemic. Clinicians are alerted to this possibility.

CHAPTER V

(a) RECOMMENDATIONS

"I realize more keenly than ever that nature is so infinitely varied in her manifestations - even in the limited domain of breast cancer", (C. D. Haagensen, 1971).

The study the first of its kind in Nigeria and probably, in West and East Africa, attempts to examine various aspects of breast diseases, particularly breast cancer. Despite limitations through inadequacy of clinical case records and other difficulties, nevertheless the study has produced much information on which general recommendation for future action and research might be based:

Census:

The last official census taken in Nigeria was 1963. Since then Nigerian population has definitely increased. It is recommended that Nigerian government should now take a new census which is needed for medical and other purposes. Knowledge of accurately estimated incidence rate and prevalence of diseases in a given population, no doubt, will add to the advancement of medical knowledge in Nigeria.

Registrations of Births and Deaths:

This should be made the government priority. Birth and Death registry should be created in both urban and rural areas of Nigeria,

and the registration should be made compulsory on national level. In the medical field it is of vital importance to obtain accurate data on frequency, age distribution and mortality date on various human diseases including cancer.

Mass Education:

There is mass ignorance on cancer as a cause of disease that kills, particularly in most rural areas of Nigeria. Mass education on various aspects of human diseases based on national level is highly desirable in most developing countries of Africa.

Organisation of Cancer Units:

The aim here is to establish a medical unit specialised in cancer chemotherapy and radiotherapy. Trained social workers should also be included to provide efficient link between the established cancer unit and the patients in any part of the Federation. This will encourage regular follow-up of patients operated upon for cancer, thus minimising the amount of cases "lost to follow-up" in a given hospital.

Mass mammography aimed at early diagnosis of mammary cancer may be undertaken on national level, under the supervision of such "cancer unit".

Cancer Registry:

This has already been established in Ibadan University Teaching Hospital since 1960. Its value has already been proved here when it is realised that this has been one of the African sources from which the International Union Against Cancer (U.I.CC) obtains its data on cancer in tropical Africa. It is however, important to stress to Nigerian government the importance of establishing such cancer registries in the various newly established University Teaching Hospitals throughout the Federation.

Cancer Research Unit:

This is of vital importance not only to Nigeria, but also to the world as a whole. The value of tumour classification is to assess cause, treatment or prognosis of a disease. The aetiology of cancer is not yet known and this is a challenging human problem facing doctors and scientists all over the world. A cancer research unit should be established by Nigerian Government throughout all the available Teaching Hospitals in Nigeria, and funds should be made available for such an honourable purpose. Africa should be in forefront now along with Europe and America, for this purpose.

A cancer research unit when established in a Teaching Hospital should aim at :

(1) Extracting and identifying all the active chemical agents in the native drugs.

(2) Ascertaining whether any of the chemical compounds may serve as a chemotherapeutic agent against cancer.

(3) Ascertaining whether any of the chemical compounds is carcinogenic to breast or any other organ of the body.

The role of "AGUNMU" and "AGBO" most commonly used in this part of Nigeria, and aflatoxin as possible carcinogens to breast needs investigation. The "milk factor" mentioned currently in relation to medullary carinoma, as well as part played by E.B. virus which is believed to be an aetiological factor in Burkitt's lymphoma, as carcinogenic agents to breast needs to be investigated. The protective role played by melanin pigments against cancer currently hypothesised needs investigation.

Such experiments as recommended are usually carried out in experimental animals. Efficient experimental animal house with trained personnel needs primarily to be established for this purpose. Although most of these recommendations are gradually taking place in various Teaching Hospitals in the Federation, there is still greater

need for the Nigerian government to allocate adequate funds for her Health Programme during the Budget. This will definitely encourage more Nigerian doctors dedicate themselves to medical re search with the aim of joining the rest of the world in research on the aetiology of cancer, thus aiding in eradicating this human scourge.

(b) CONCLUSION

The current study attempts to analyse various aspects of breast diseases particularly breast cancer in Nigeria, in order to provide data on neoplasia from tropical Africa with the hope that striking differences such as exposure to environmental factors or genetic factors may help to lead to the hypothesis on aetiology of breast cancer throughout the world. It is evident from the current study that breast cancer occurs in all races of the world, but tends to have a higher incidence rate in the white than in the coloured races; to have a higher incidence rate in females than in males throughout the world, and occurs more in the temperate than in the tropical zones of the world. Its epidemiological study has demonstrated that women who breast feed their children are less susceptible to breast cancer than women who do not. The low incidence of breast carcinoma currently observed in both Nigerian and Japanese women, who naturally breast feed their children, and the finding that medullary carcinoma, which is noted for its good prognosis, and has a higher incidence in these two nations that commonly breast feed their babies, are perhaps related to breast feeding. Prolonged breast feeding is therefore advocated for all women throughout the world.

Deeper studies on the currently observed striking differences in breast cancer incidence between the coloured and white races of the world are recommended as such may lead one nearer to the understanding of aetiology of breast cancer throughout the world.

ACKNOWLEDGEMENTS

When I first came to the Department of Pathology, University College Hospital, Ibadan, Nigeria in July, 1974, Professor Olufemi Williams, then the head of the department, suggested that I should write thesis on 'Breast Carcinoma in Nigeria' for Glasgow University. At first I wondered on what I could write on breast diseases that had never been written before in the Western literature, but on second thought, I agreed. He travelled from Nigeria (Ibadan) to Britain (Glasgow), where he contacted the late Professor A.I. Haddow, then the administrative Dean, Faculty of Medicine, University of Glasgow, and arranged for me to write this thesis. I wrote to my alma mater, Glasgow University, Scotland and I was enrolled for the M.D. Thesis for Glasgow University on 3rd May, 1976. From then on Professor Williams had made available to me his department and all the materials obtained for this work. For all these I am deeply indebted to him.

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BREAST CANCER IN NIGERIA

THESIS

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APPENDIX 1: MAP OF NIGERIA.

PLATE 1.

MEDICAL CENTERS IN NIGERIA.

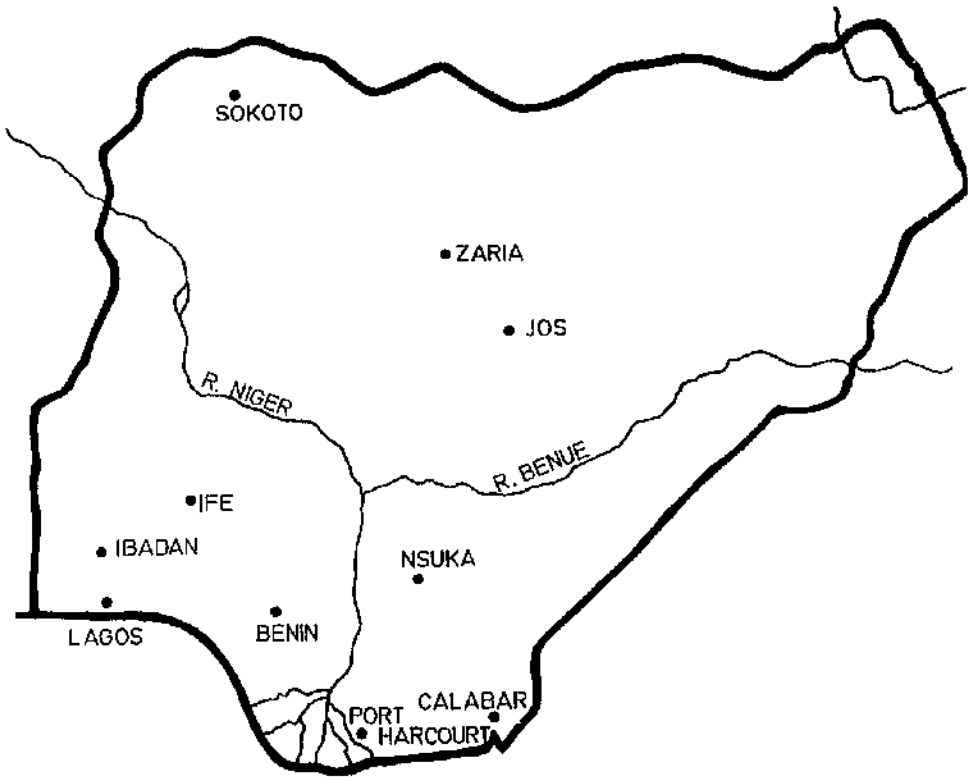


FIGURE 1: University College Hospital (U.C.H.) is cited in Ibadan, the capital city of Western Nigeria.

APPENDICES 2-6: GRAPHS ON VARIOUS EPIDEMIOLOGICAL ASPECTS OF BREAST CANCER.

2 PLATE 2.

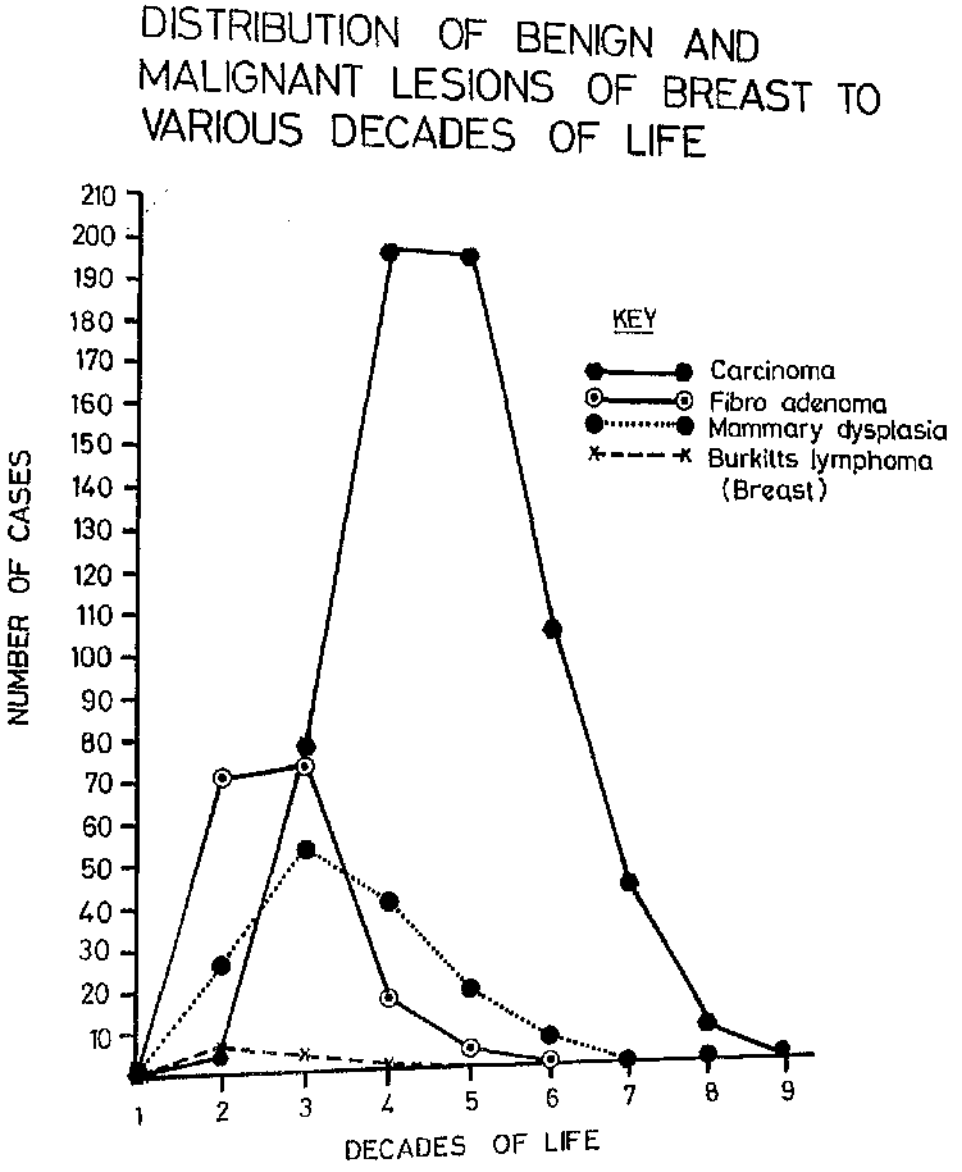


FIGURE 2: Fibroadenomas are second to carcinomas as the commonest causes of breast lumps in Nigeria.

ANNUAL INCIDENCE OF BREAST NEOPLASIA IN NIGERIA.

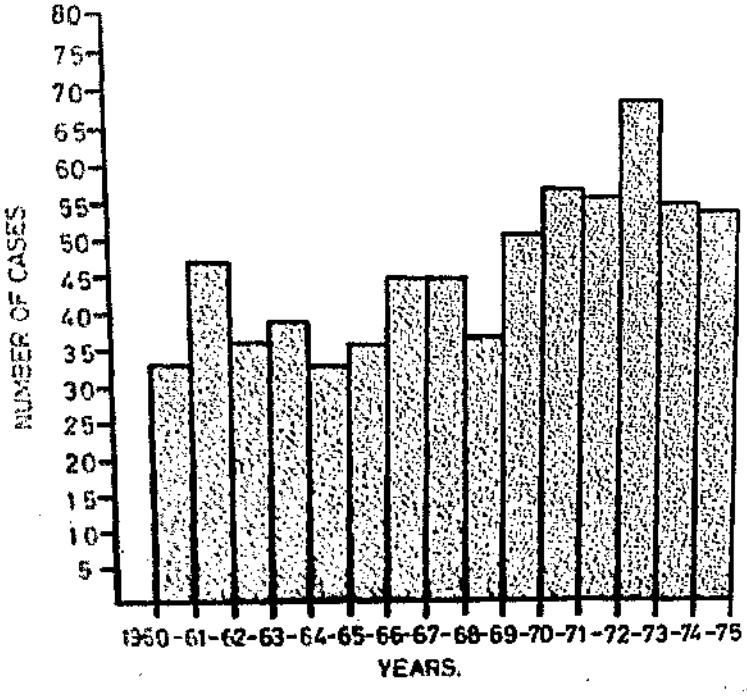


FIGURE 3: Uncorrected annual incidence of breast cancer. Observe increased incidence for the years 1969-75 compared with 1960-69.

PLATE 4.

AGE SPECIFIC DISTRIBUTION OF BREAST CARCINOMA PER 100,000 OF IBADAN POPULATION (FEMALE).

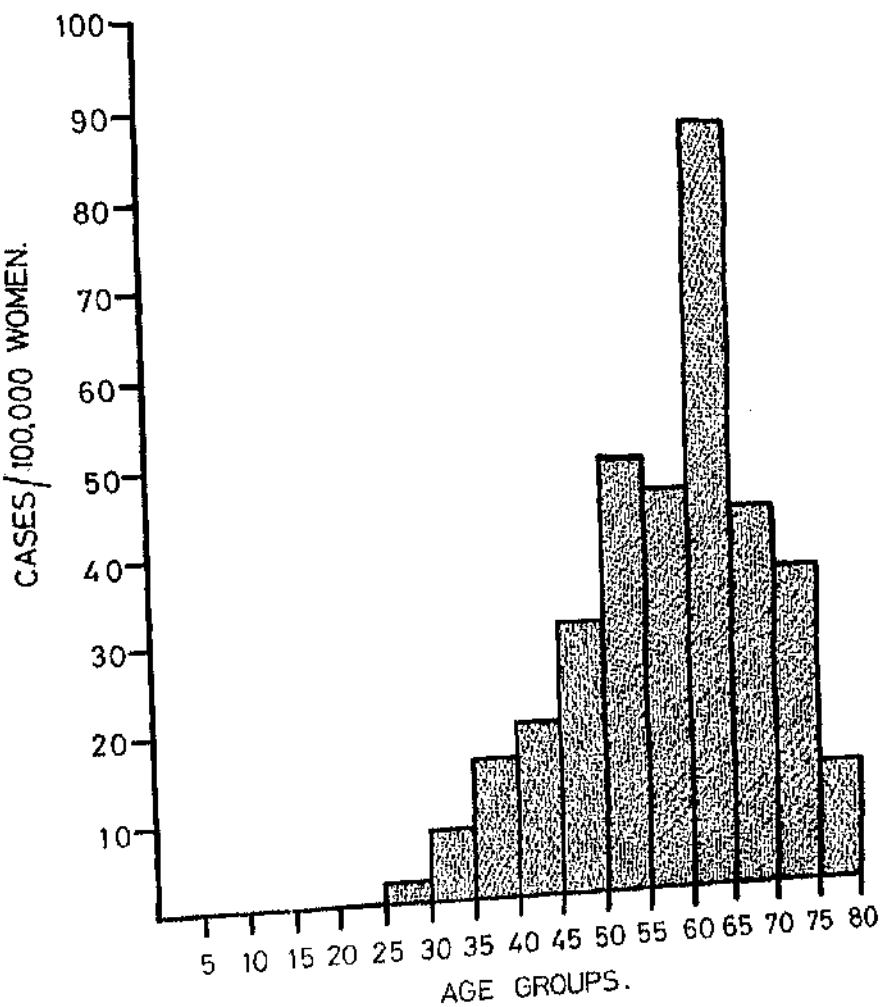


FIGURE 4: **Annual incidence of breast cancer per 100,000 of population rises as population falls with rising age.**

PLATE 5.

DISTRIBUTION OF GRAVIDA AMONGST 191 FERTILE CANCER PATIENTS AND 196 CONTROL.

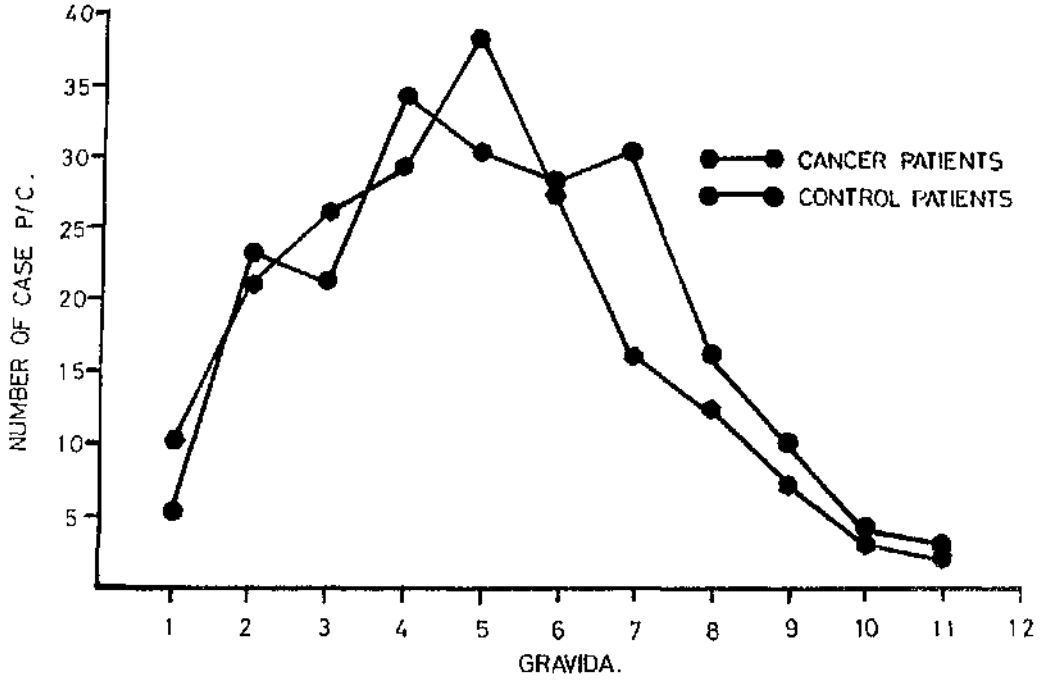


FIGURE 5: Control patients have a greater number of pregnancies per patient than the breast cancer patients.

PLATE 5a.

NUMBER OF YEARS SPENT BREAST FEEDING ONE CHILD BY CANCER AND CONTROL PATIENTS.

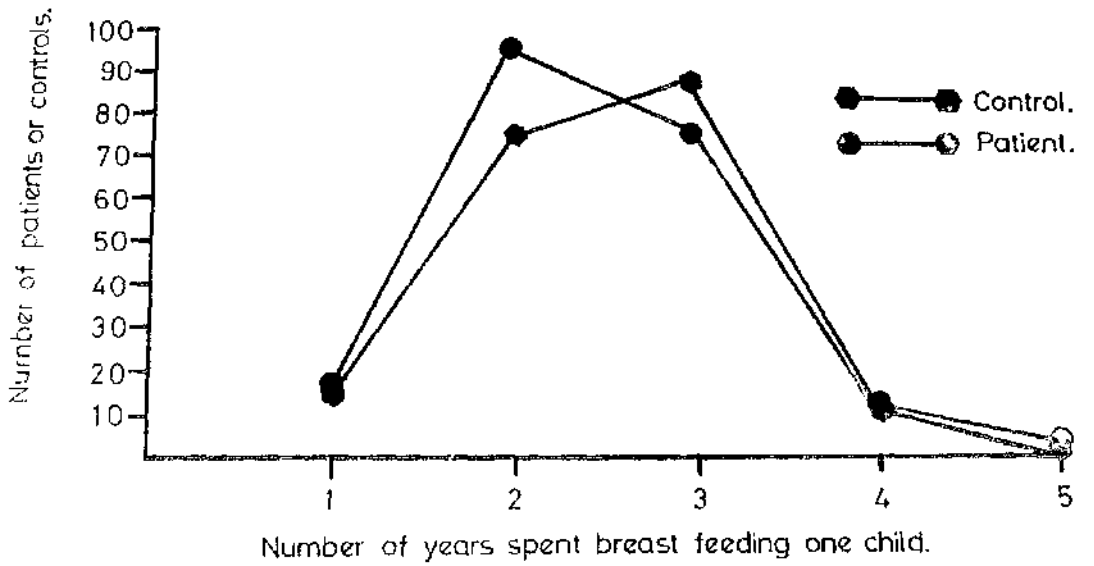


FIGURE 5a: Both cancer and control patients have the same breast feeding pattern.

PLATE 6.

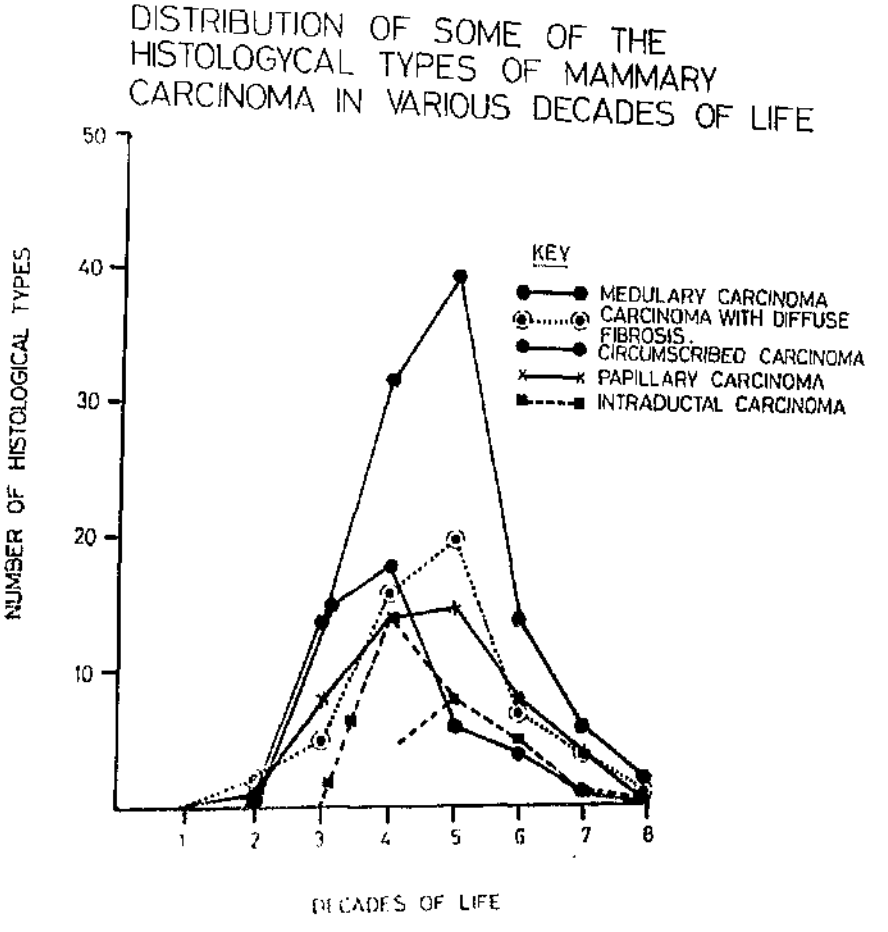


FIGURE 6: Medullary carcinoma is predominantly the commonest histological type of breast carcinoma from 2nd to 8th decade of life.

APPENDICES 7-10: GENERAL MICROSCOPIC FEATURES OF BREAST CANCER.

PLATE 7.

Microcalculi In Breast Cancer

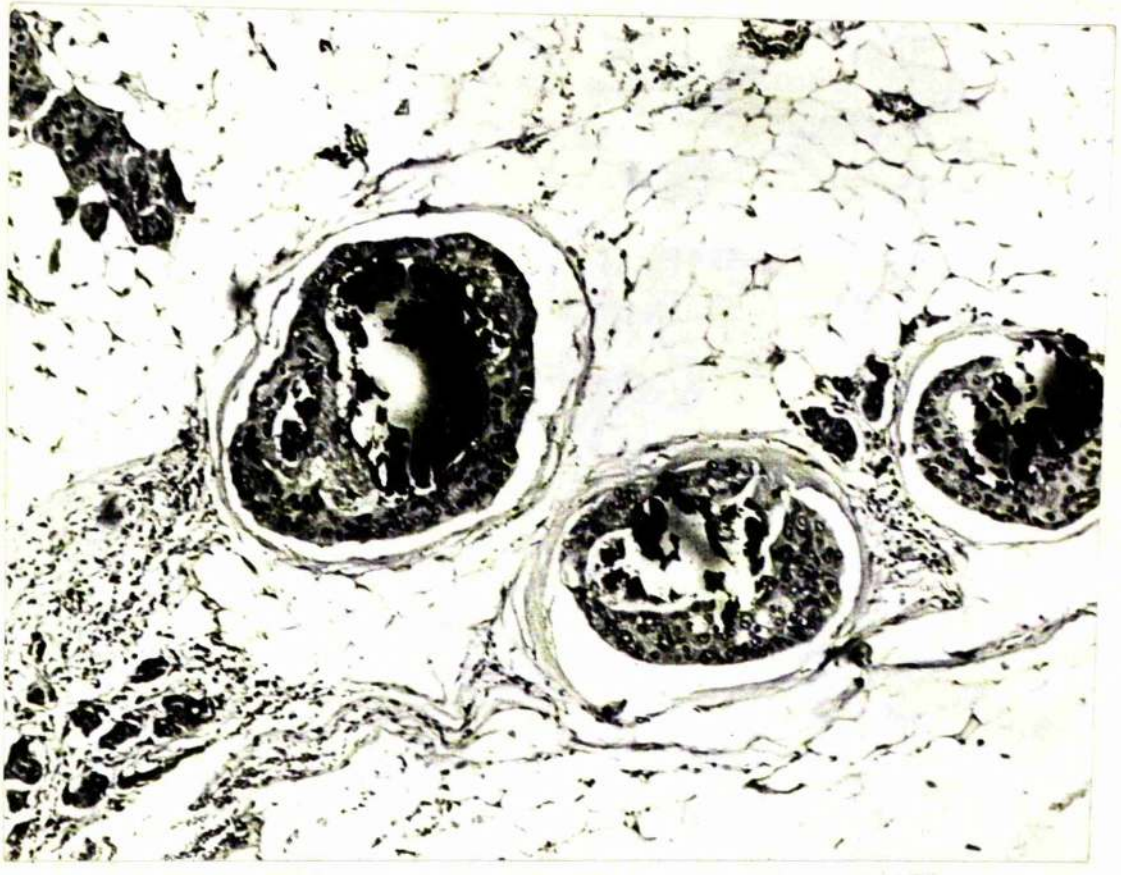


FIGURE 7: Central areas of calcification in solid intraductal carcinoma.

Haematoxylin and eosin X 198.

PLATE 8.

Microcalculi In Breast Cancer

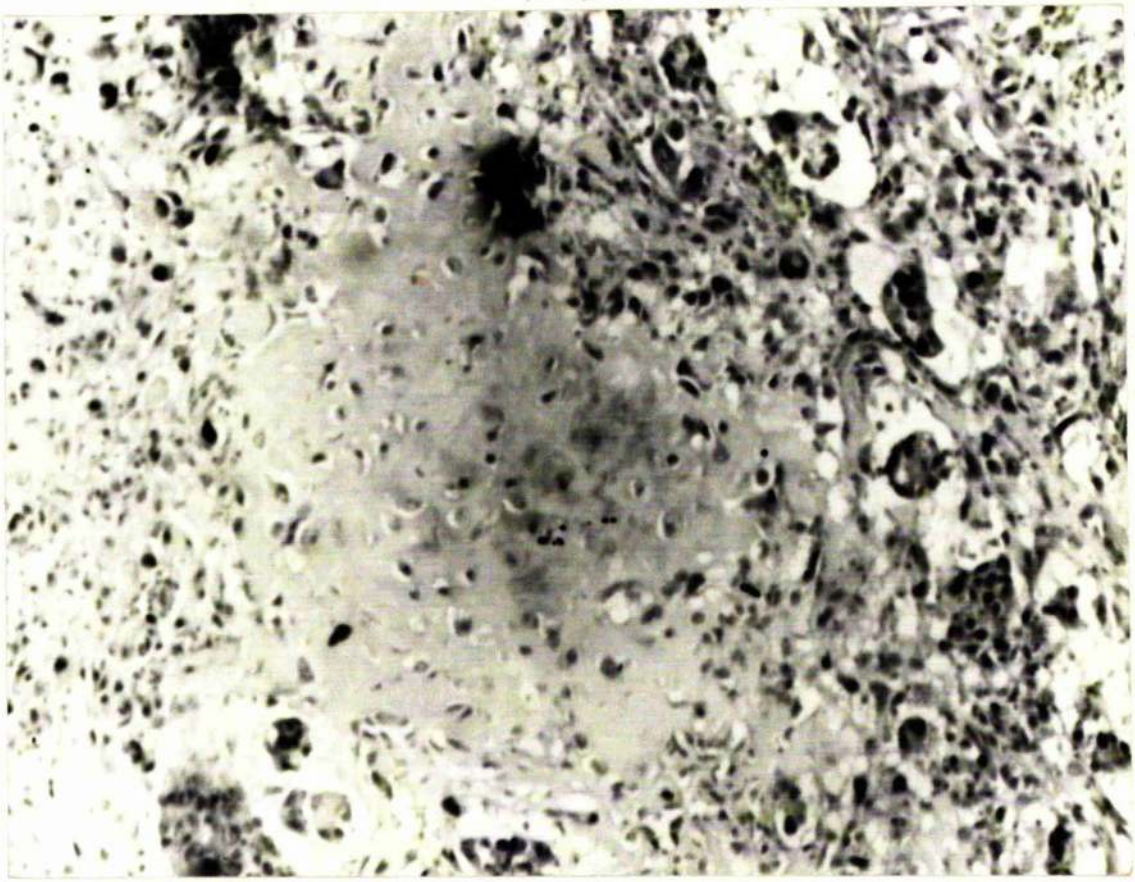


FIGURE 8: Focus of calcification in carcinoma of breast with osseous/cartilagenous metaplasia.

Haematoxylin and eosin X 100.

PLATE 9.

Depigmentation Phenomenon

FIGURE 9: Melanocytes contain non-aggregated melanin granules in a normal skin overlying a deeply situated cancer below.

Haematoxylin and eosin X 100.

PLATE 10.

Depigmentation Phenomenon

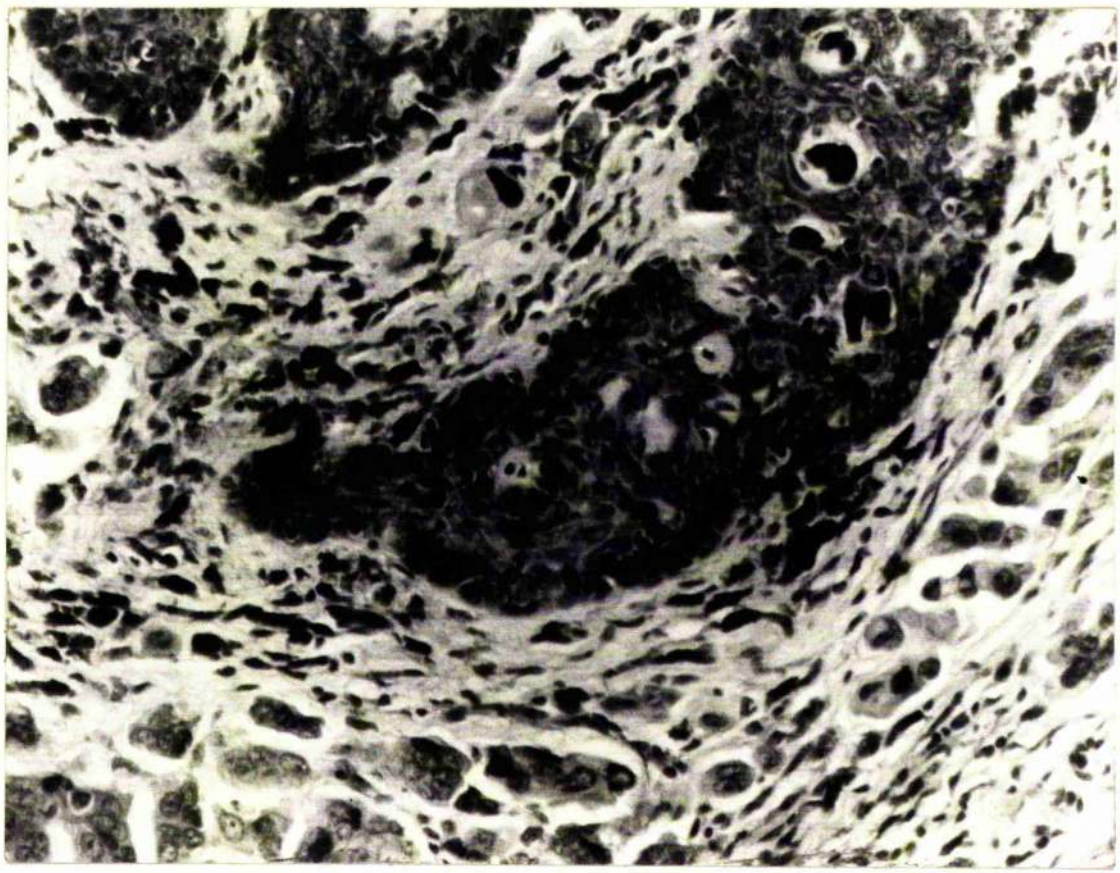


FIGURE 10: **Invasive carcinoma advancing towards the epidermal border. Melanin granules aggregated in melanocytes, some forming melanin lakes in epidermis.**

Haematoxylin and eosin X 200.

PLATE 11.

Depigmentation Phenomenon

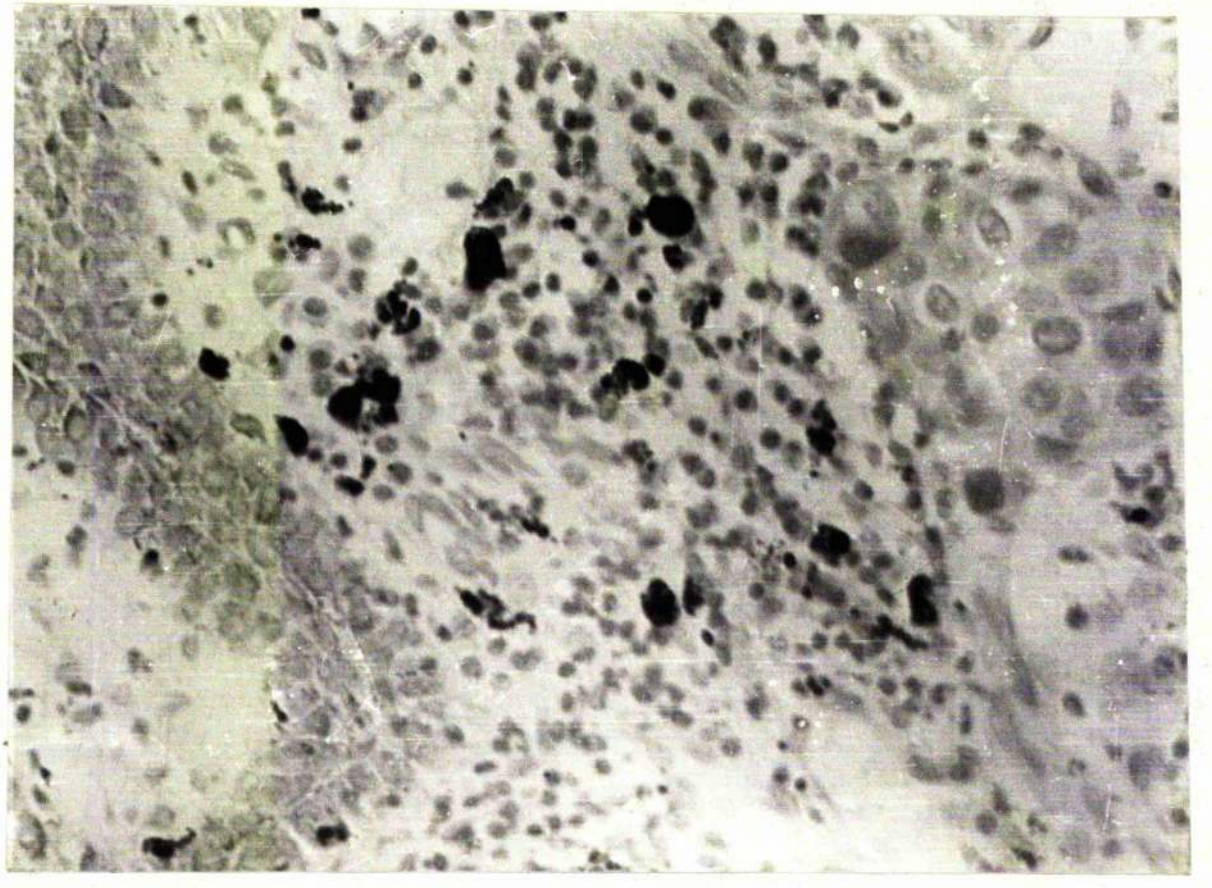


FIGURE 11: Macrophages laden with melanin granules along with lympho/plasma cells interposed between depigmented epidermis (left) and carcinoma (right).

Haematoxylin and eosin X 200.

PLATE 12.

Depigmentation Phenomenon

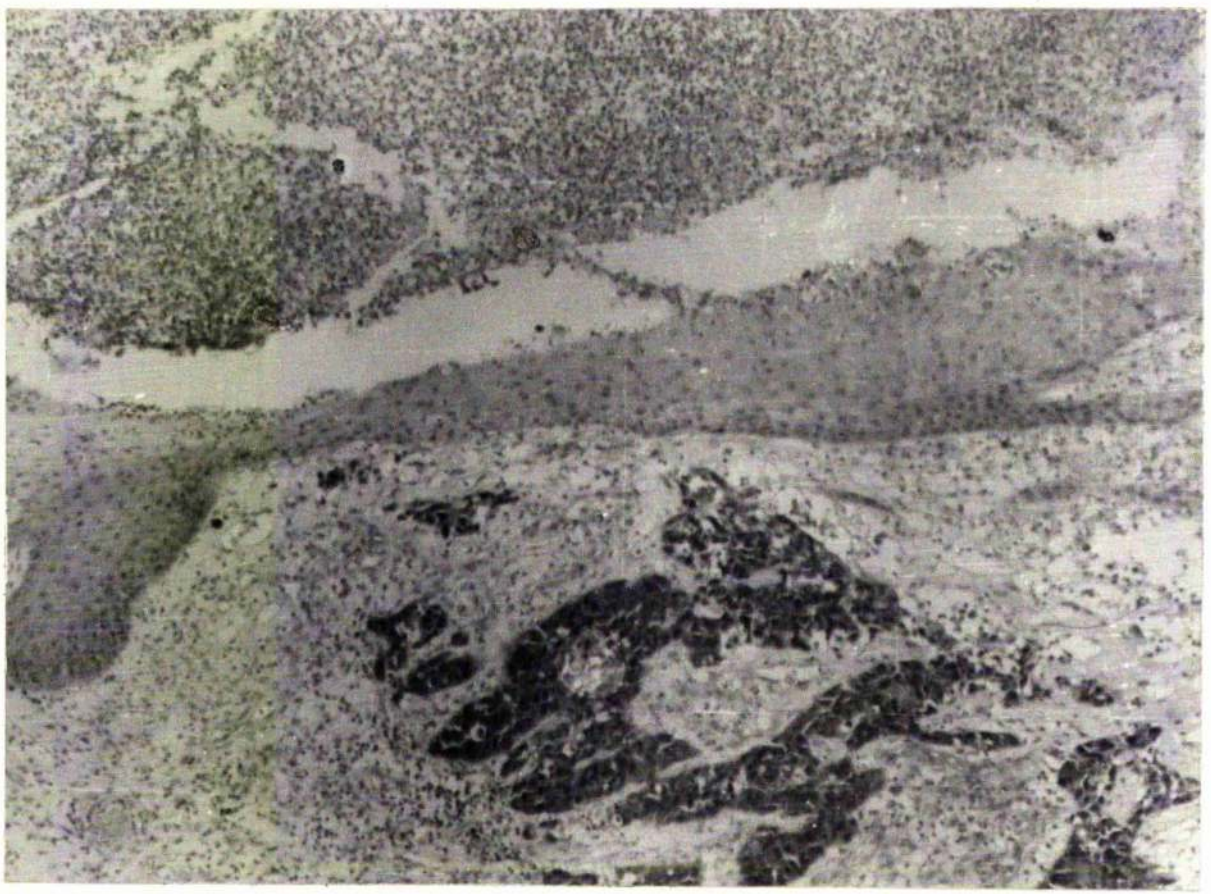


FIGURE 12: Shows almost completely depigmented epidermis (above), being invaded by cancer.

Haematoxylin and eosin X 200.

PLATE 13.

Depigmentation Phenomenon

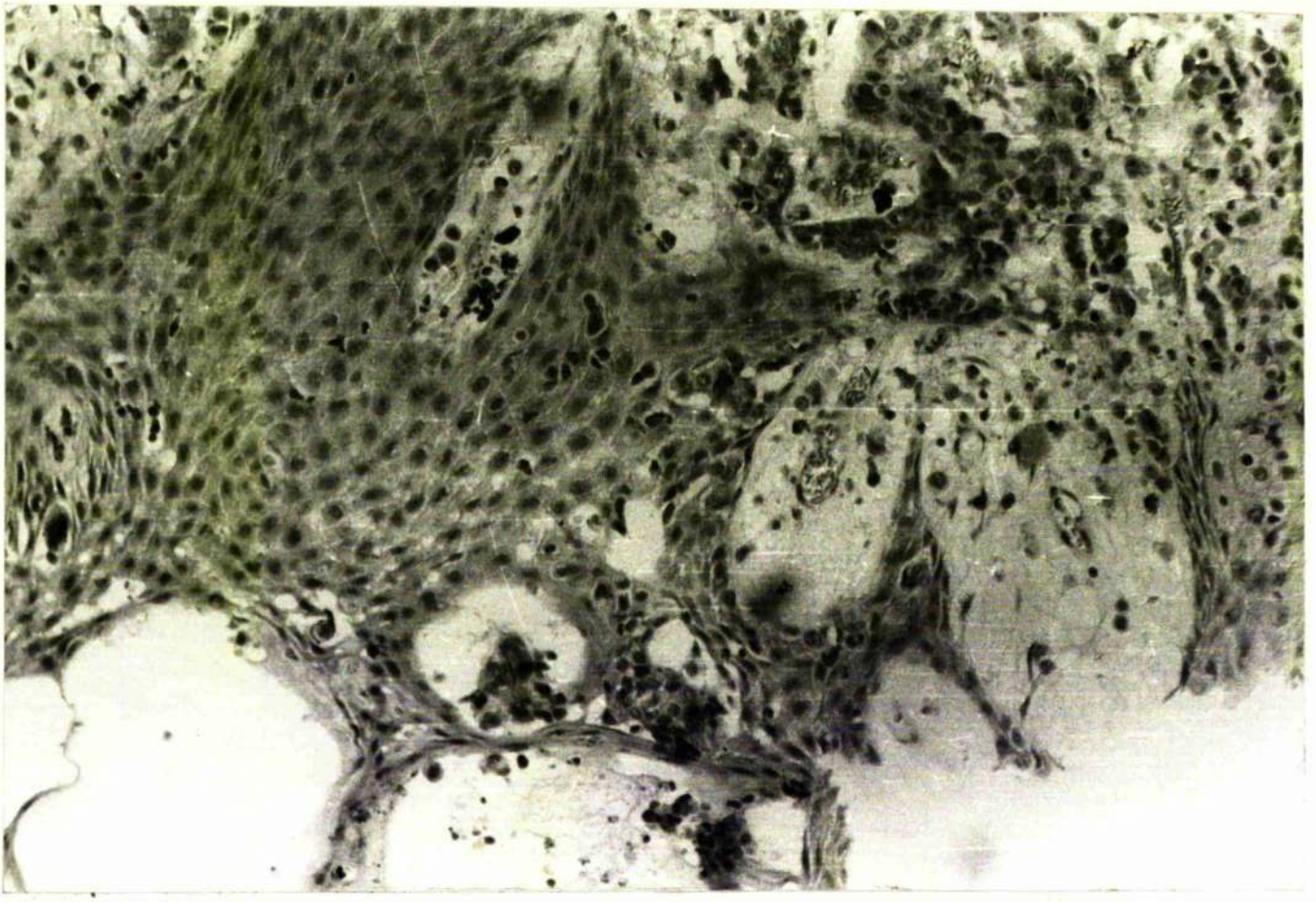


FIGURE 13: Depigmented epidermis, invaded by nests of carcinoma cells.

Haematoxylin and eosin X 200.

PLATE 14.

Depigmentation Phenomenon

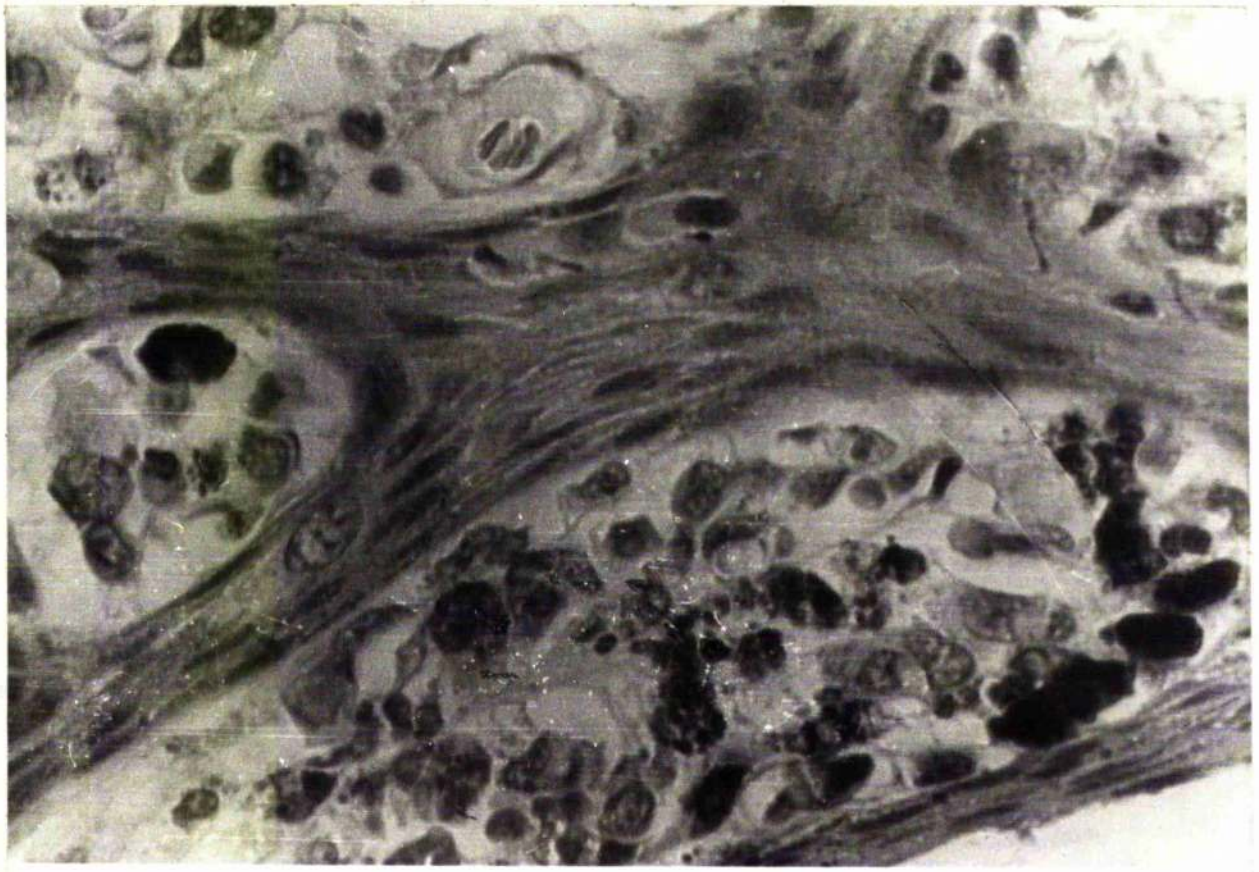


FIGURE 14: Nests of invading malignant cells laden with phagocytosed melanin granules mimicking intraepidermal malignant melanoma.

Haematoxylin and eosin X 200.

PLATE 15.

Depigmentation Phenomenon

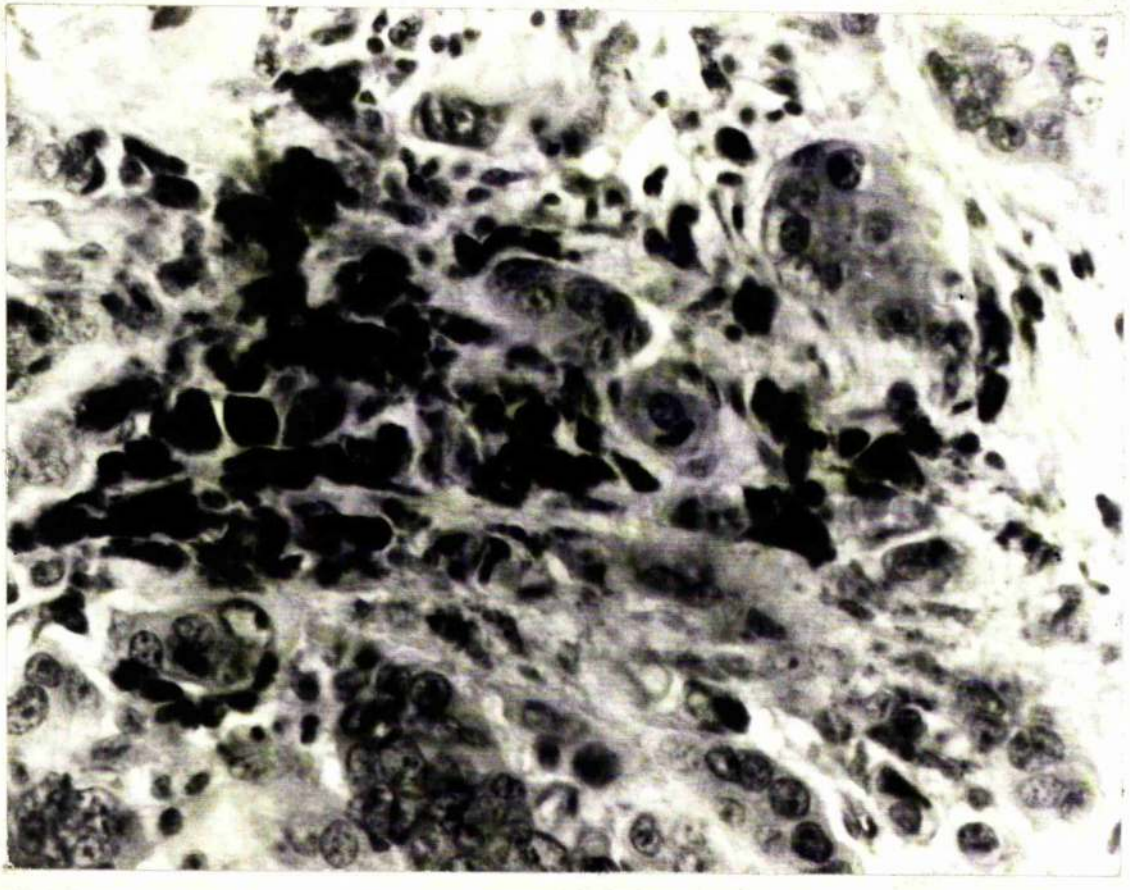


FIGURE 15: Melanin granules are phagocytosed by histiocytes and malignant cells in the tumour centre.

Haematoxylin and eosin X 200.

PLATE 16.

Depigmentation Phenomenon

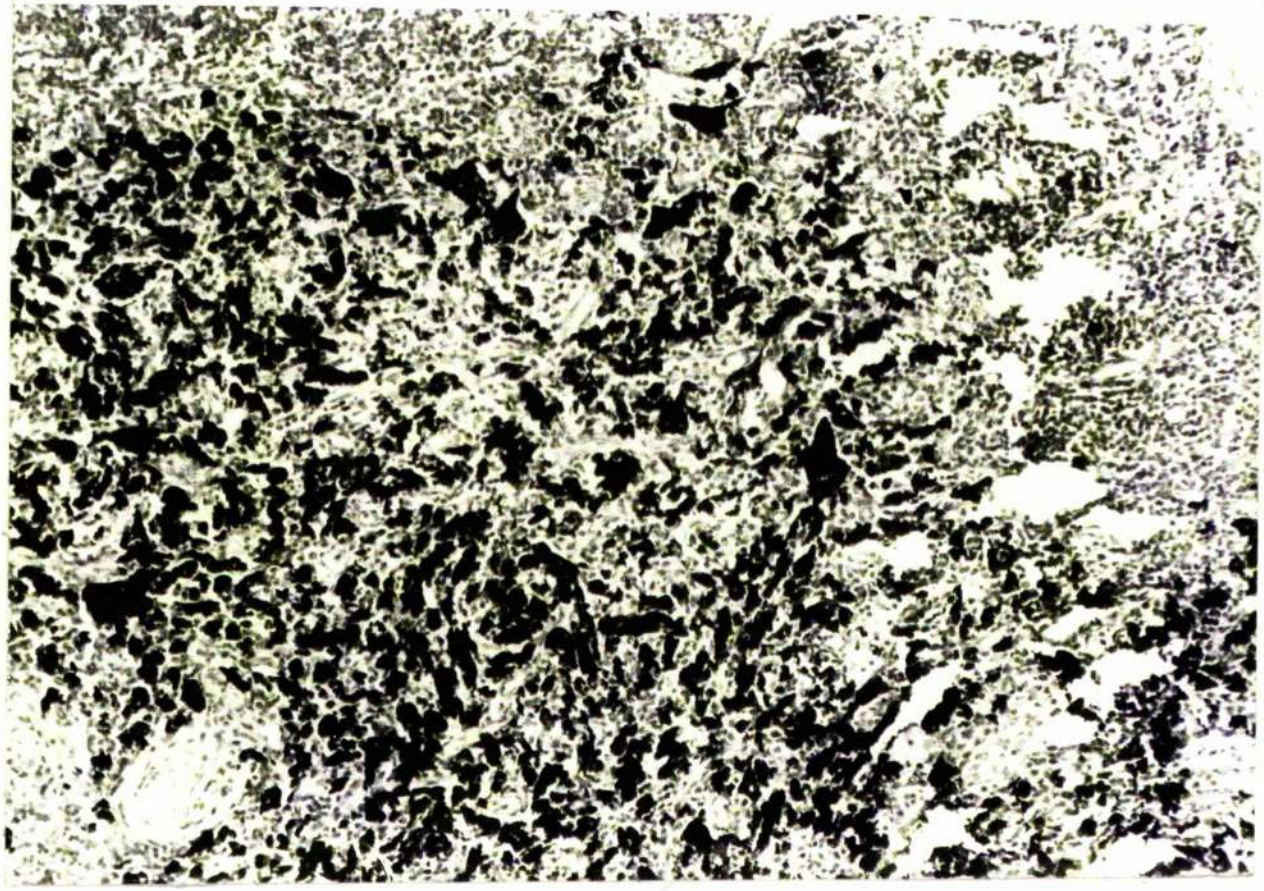


FIGURE 16: Lymph node draining such invaded depigmented skin is packed with melanin laden histiocytes.

Haematoxylin and eosin X 100.

PLATE 17.

Lymphatic Tumour Emboli

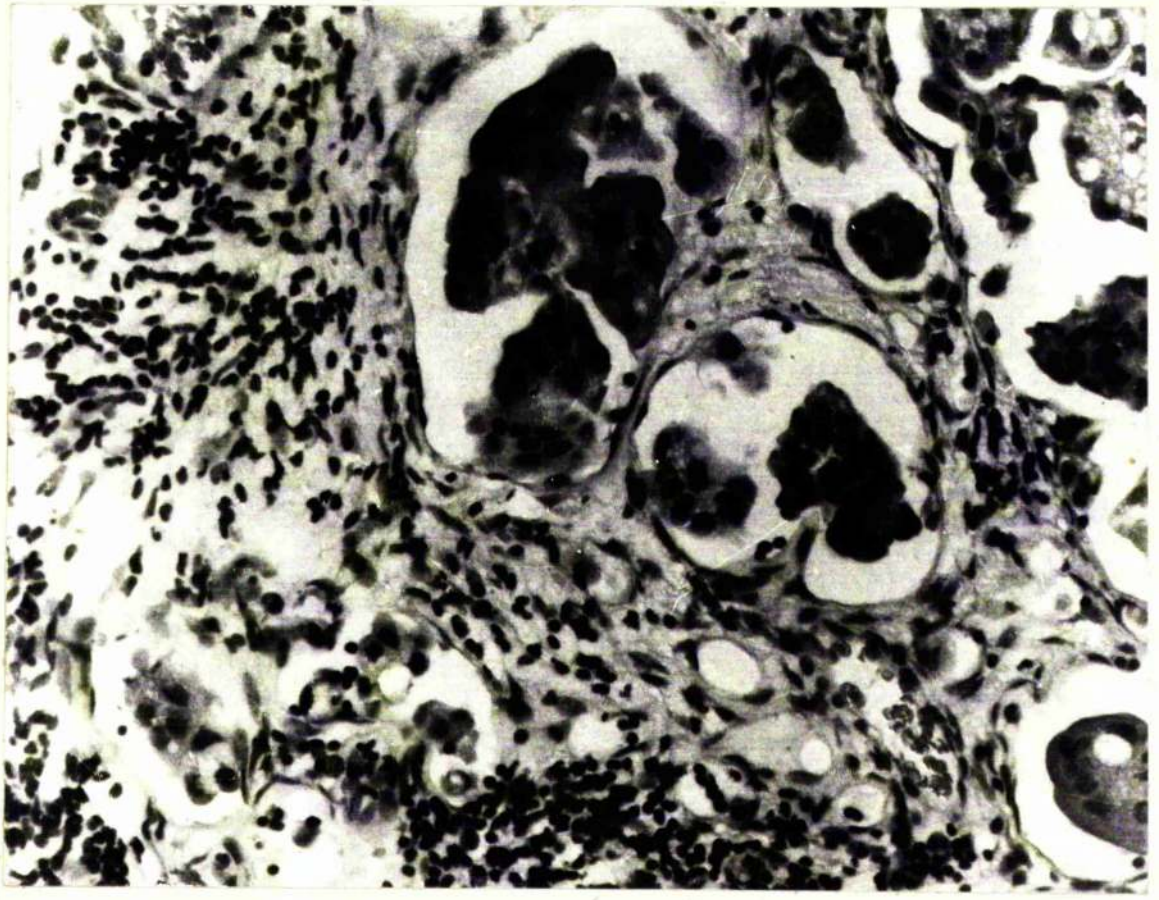


FIGURE 17: Nest of malignant coreless papillary carcinoma in dilated lymphatic vessel.

Haematoxylin and eosin X 200.

PLATE 18.

Lymphatic Tumour Emboli

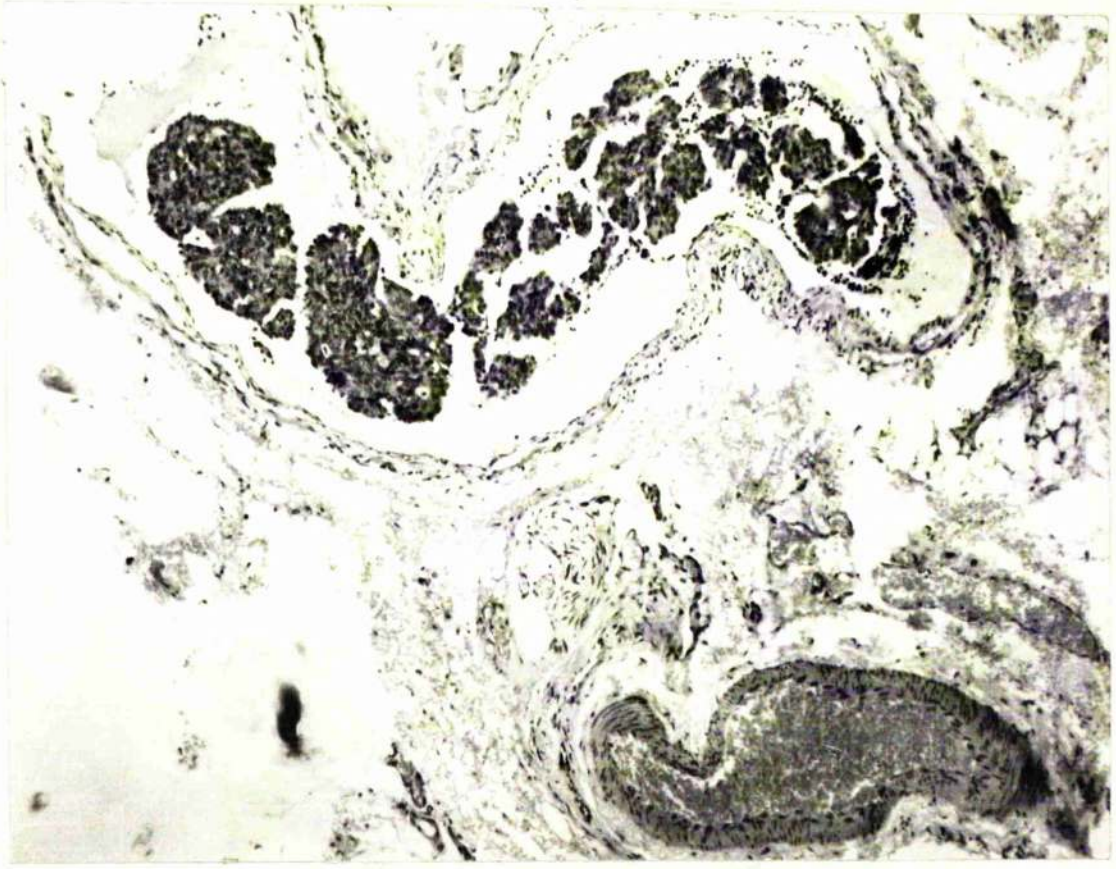


FIGURE 18: **Islets of malignant cells in grossly** dilated lymphatic vessel.

Haematoxylin and eosin X 90

APPENDIX 11: RELATIONSHIP OF BENIGN TO MALIGANT BREAST LESIONS.

PLATE 19.

Secretory Carcinoma

FIGURE 19: An area of intracanalicular fibroadenoma from mastectomy specimen of 20-year old woman.

Haematoxylin and eosin X 70.

PLATE 20.

Secretory Carcinoma

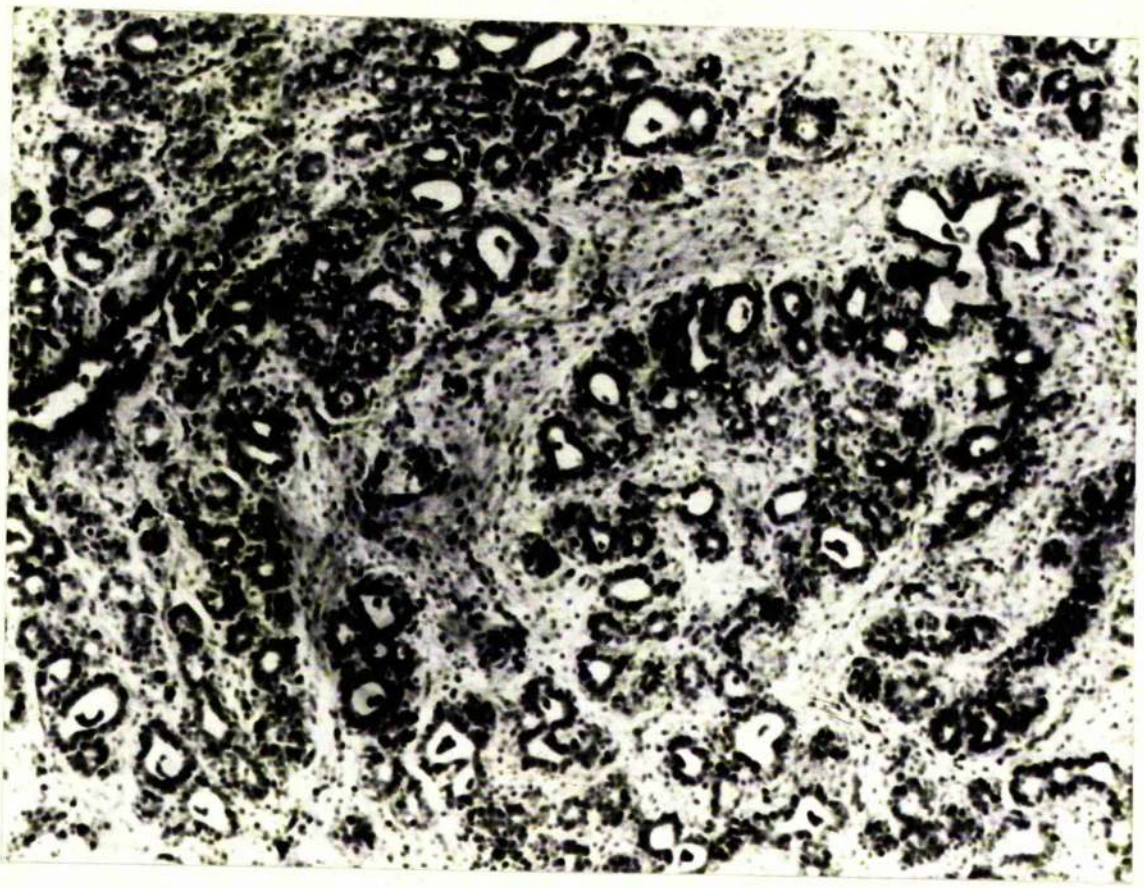


FIGURE 20: **Another area from same specimen as fig. 19 showing hyperplastic and dysplastic ductal epithelial cells.**

Haematoxylin and eosin X 70.

PLATE 21.

Secretory Carcinoma

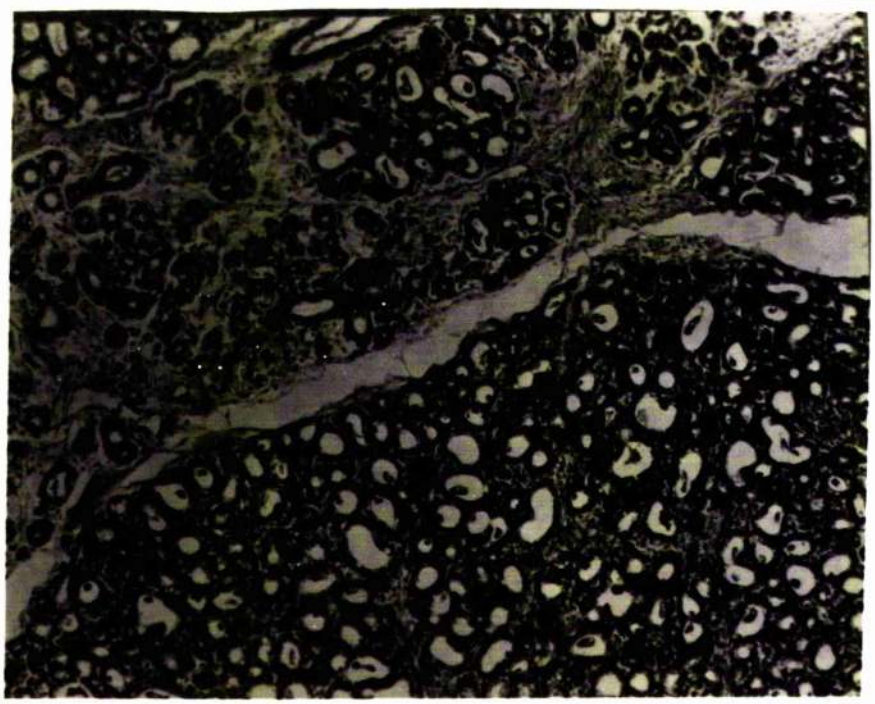


FIGURE 21: Another area from same specimen as fig. 19 showing dysplastic area above, and secretary carcinoma below.

Haematoxylin and eosin X 70.

PLATE 22.

Secretory Carcinoma

FIGURE 22: High-power view of fig 21, (secretory carcinoma). The malignant cells are vesicular.

Haematoxylin and eosin X 700.

PLATE 23.

Malignant Giant Fibroadenoma

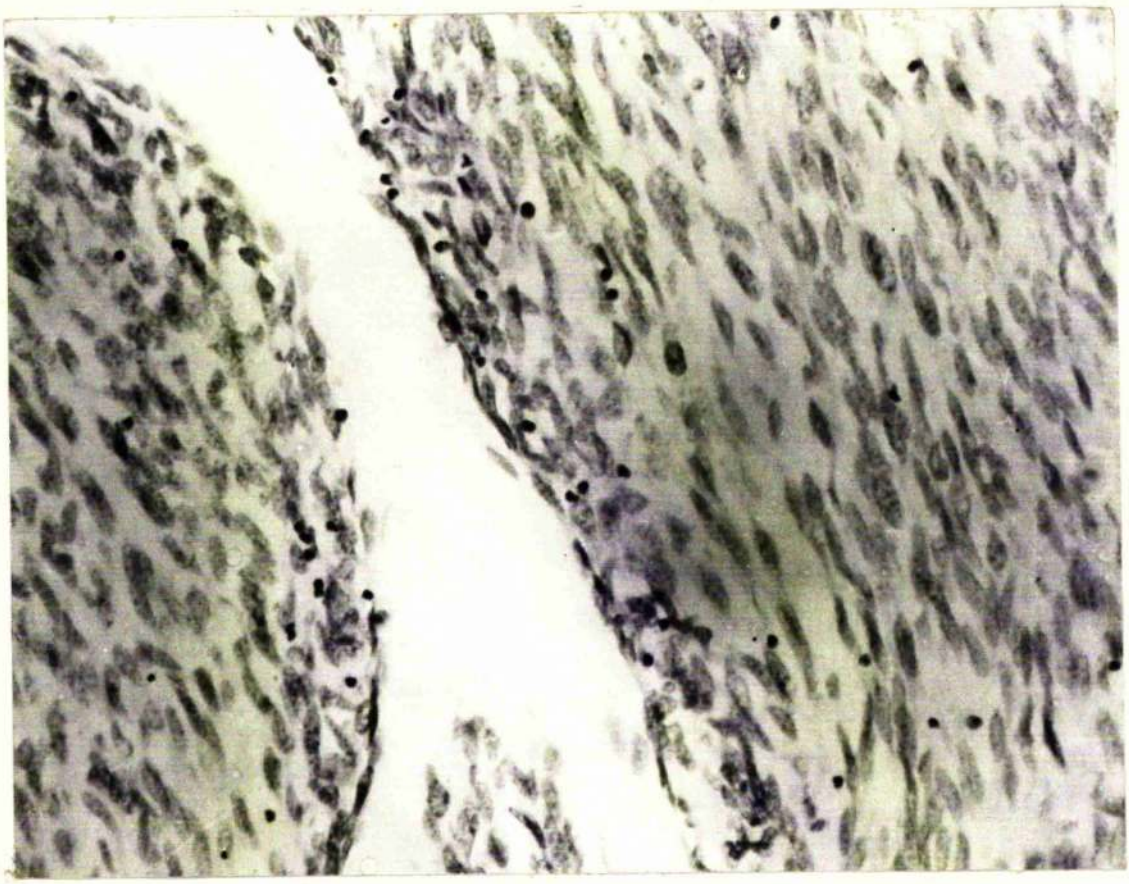


FIGURE 23: Malignant giant fibroadenoma with dilated cystic space lined by flattened epithelial cells.

Haematoxylin and eosin X 200.

PLATE 24.

Malignant Giant Fibroadenoma

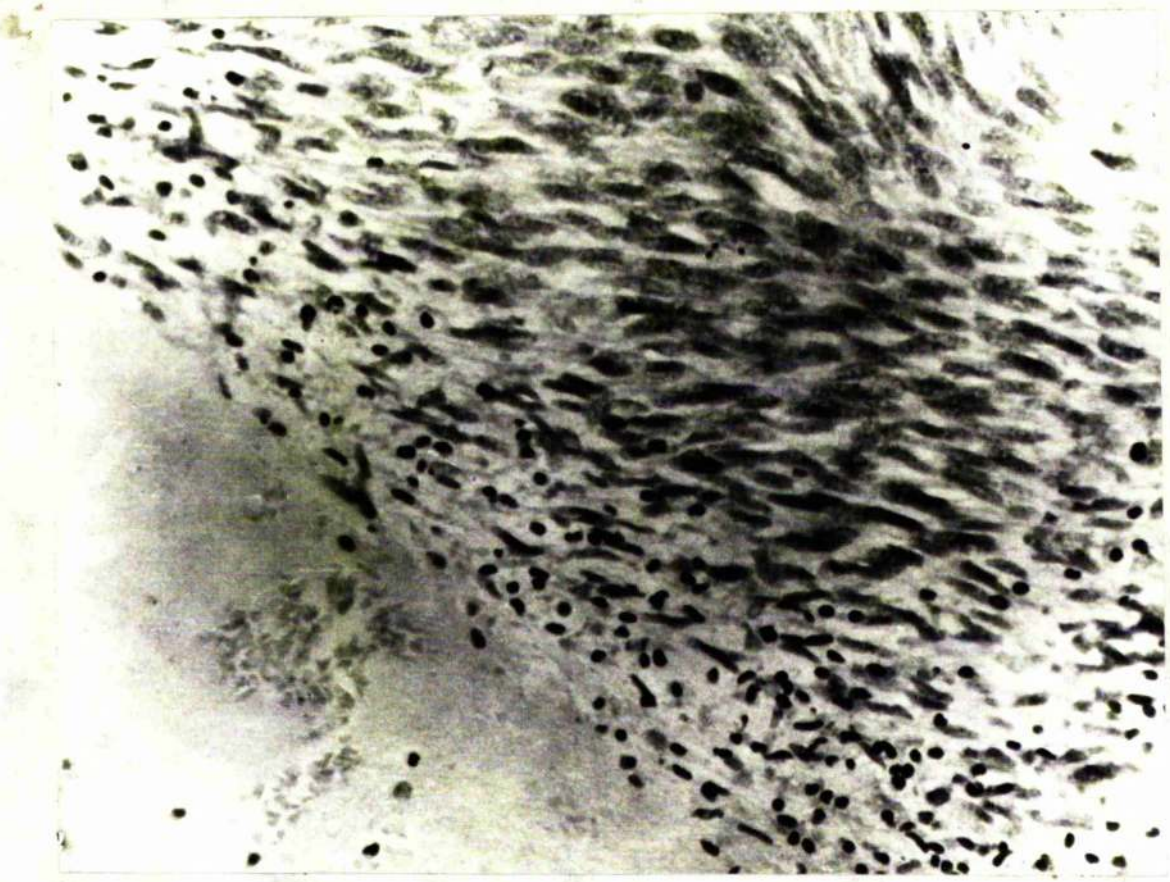


FIGURE 24: Area of necrosis in malignant giant fibroadenoma.

Haematoxylin and eosin X 200.

PLATE 25.

Gynaecomastia

FIGURE 25: Gynaecomastia. Proliferating ducts in markedly desmoplastic stroma.

Haematoxylin and eosin X 200.

PLATE 26.

Gynaecomastia

FIGURE 26: Abortive glandular lobule formation by proliferating ducts in gynaecomastia.

Haematoxylin and eosin X 100.

PLATE 27.

Gynaecomastia

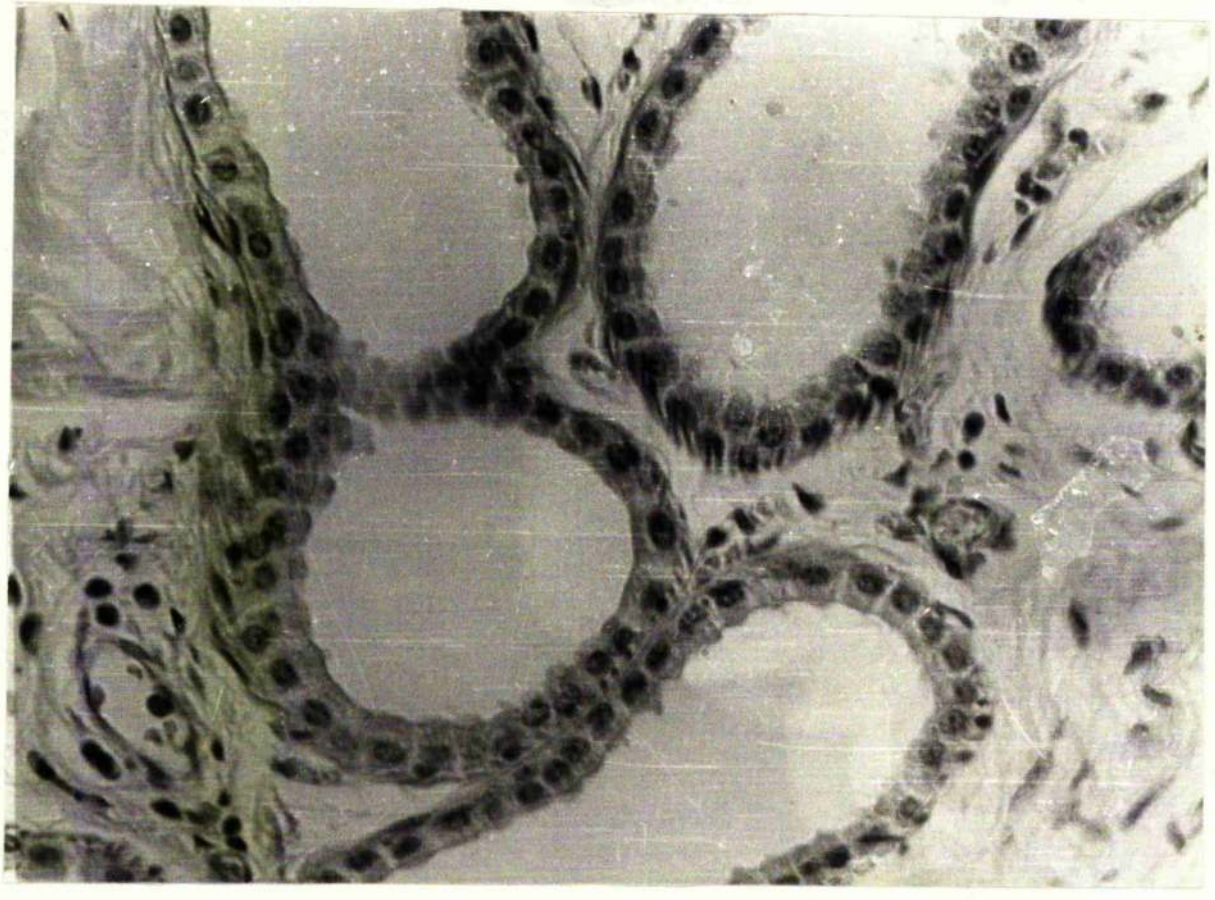


FIGURE 27: Apocrine metaplasis of ductal epithelial cells in gynaecomastia.

Haematoxylin and eosin X 290.

PLATE 28.

Gynaecomastia

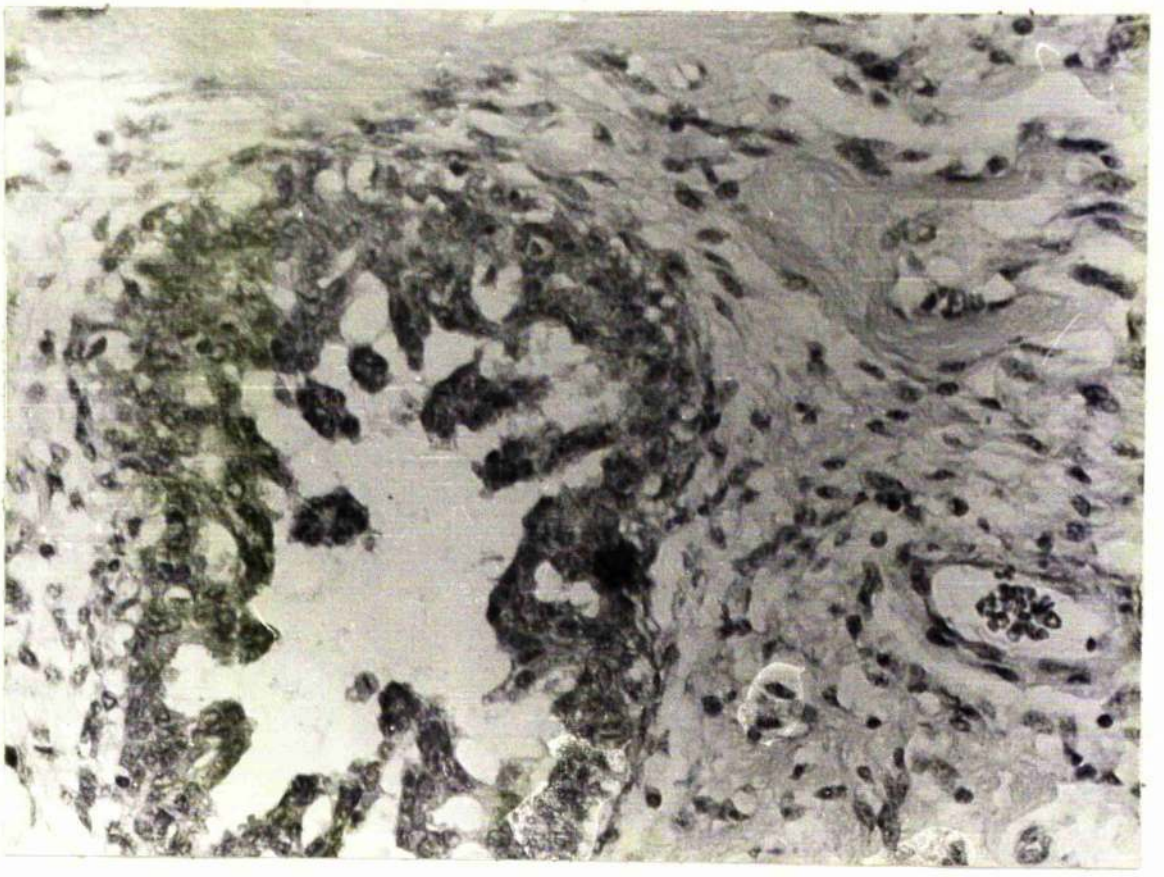


FIGURE 28: Intraductal papillary carcinoma in gynaecomastic breast of a 38-year old patient.

Haematoxylin and eosin X 200.

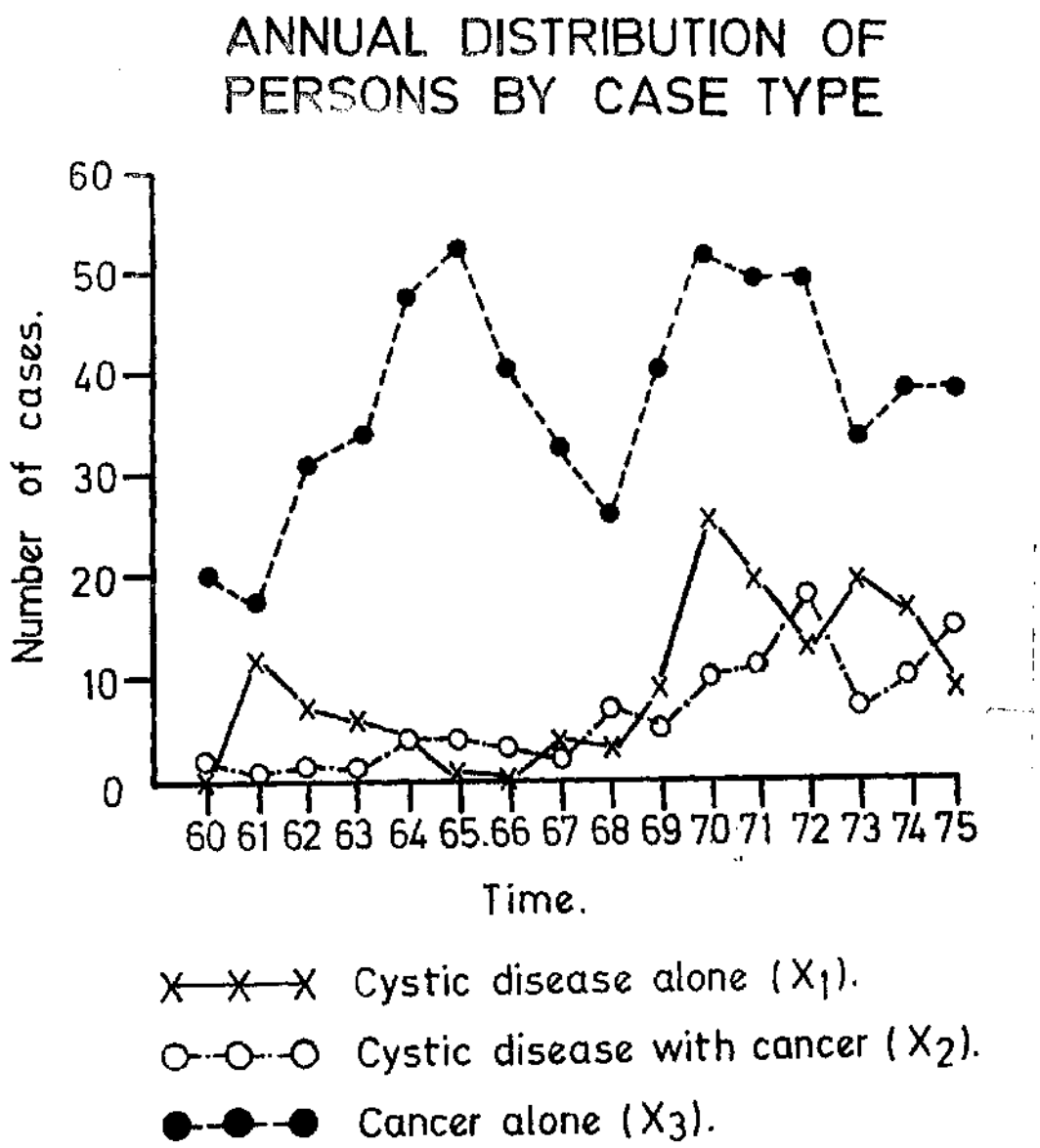


FIGURE 29: Cystic disease alone (X_1), cystic disease with cancer (X_2) and cancer alone (X_3) all have similar distribution pattern.

SCATTER DIAGRAM OF CYSTIC DISEASE ONLY + CYSTIC DISEASE WITH CARCINOMA.

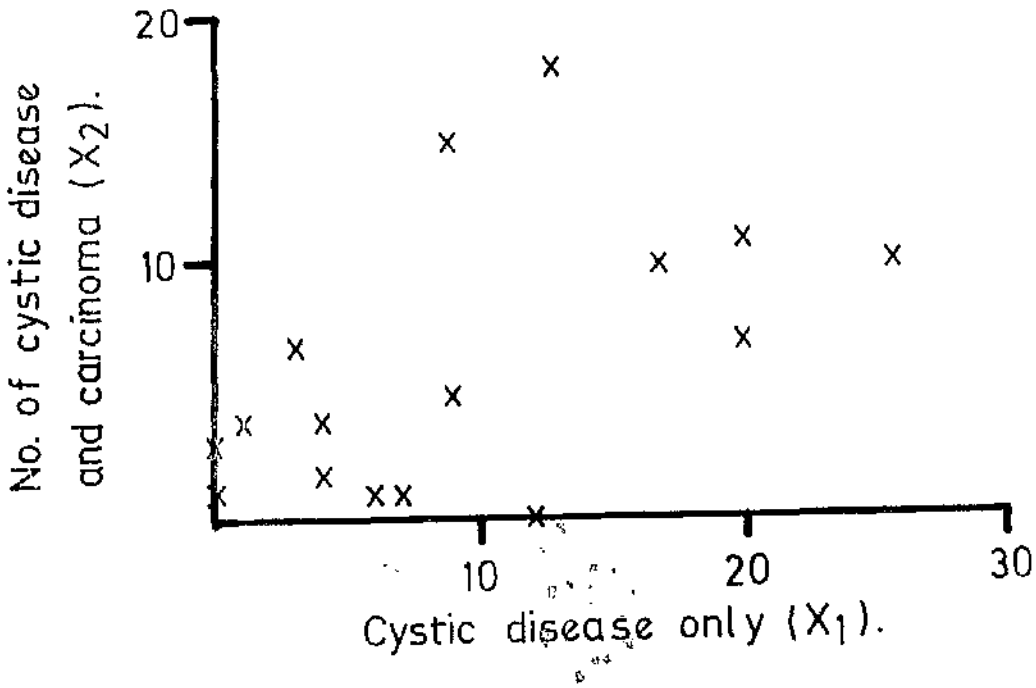


FIGURE 30: The scatter diagram is linear in pattern, for the two case-types.

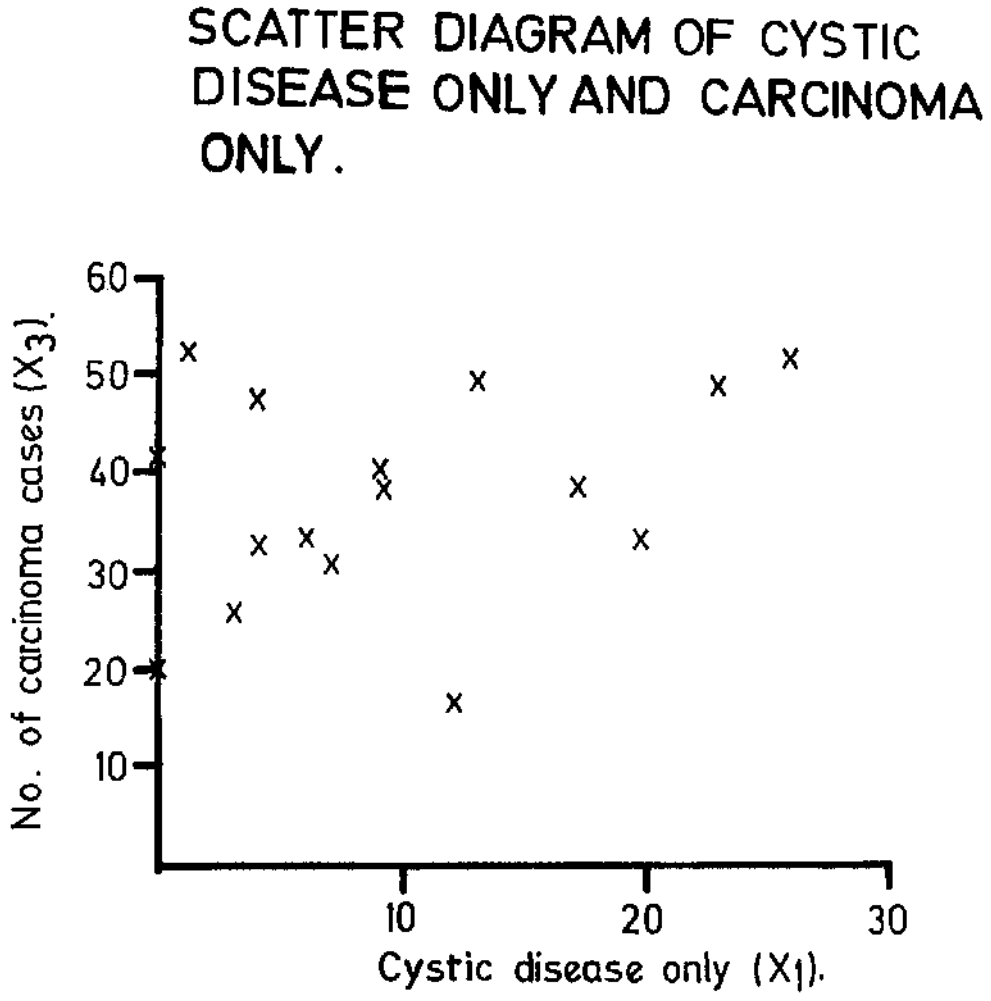


FIGURE 31: The scatter diagram is also linear in pattern as in Fig. 30, for the two case types, (X_3) and (X_1).

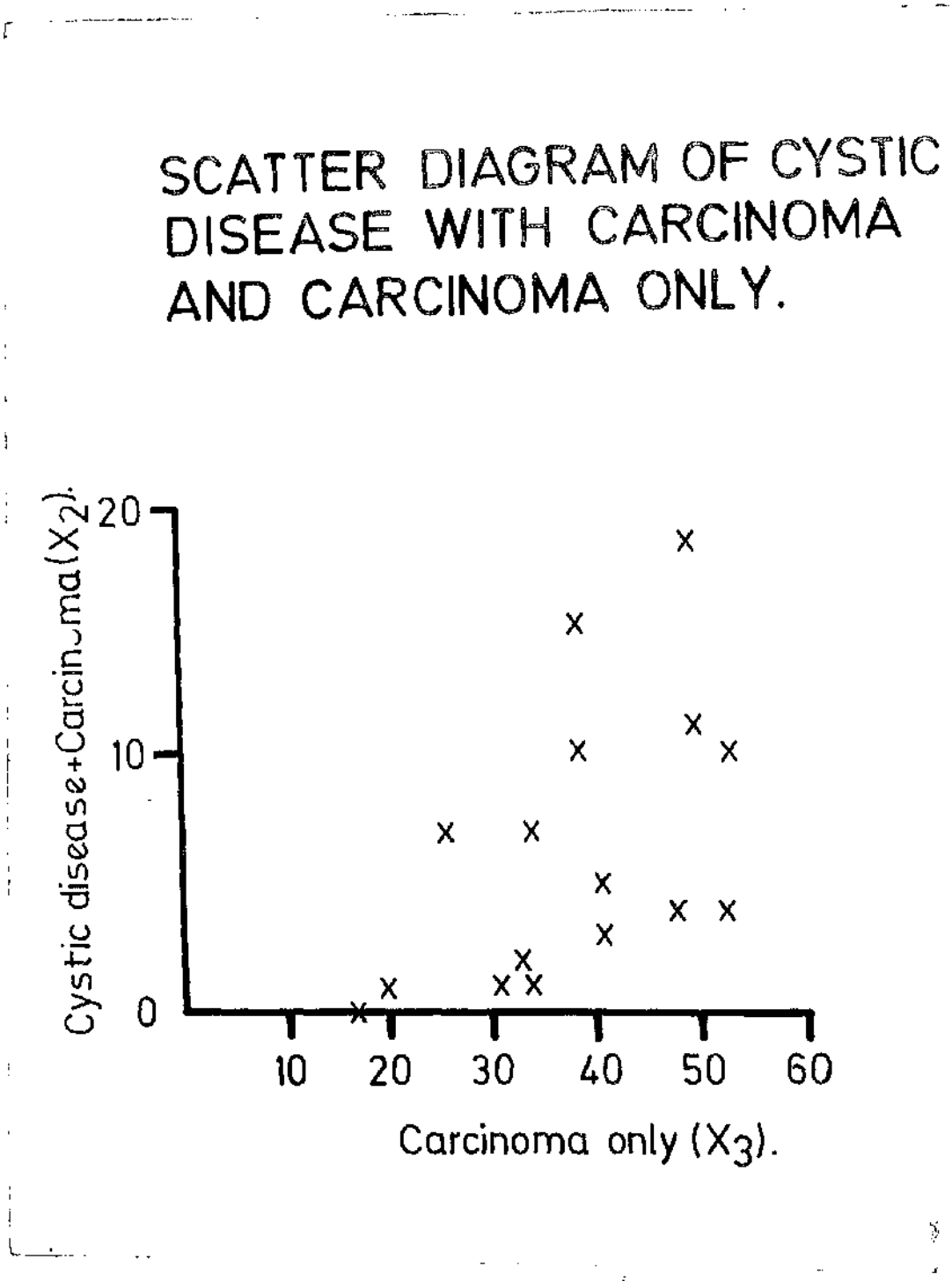


FIGURE 32: The scatter diagram is also linear in pattern as in figs. 30 and 31, the two case-types (X_2) and (X_3).

APPENDICES 12-18: SPECTRUM OF HISTOLOGICAL TYPES OF BREAST CANCER.

PLATE 33.

Lobular Carcinoma

FIGURE 33: Fibrocystic disease of the breast with occult lobular carcinoma in situ above.

Haematoxylin and eosin X 100.

PLATE 34.

Lobular Carcinoma

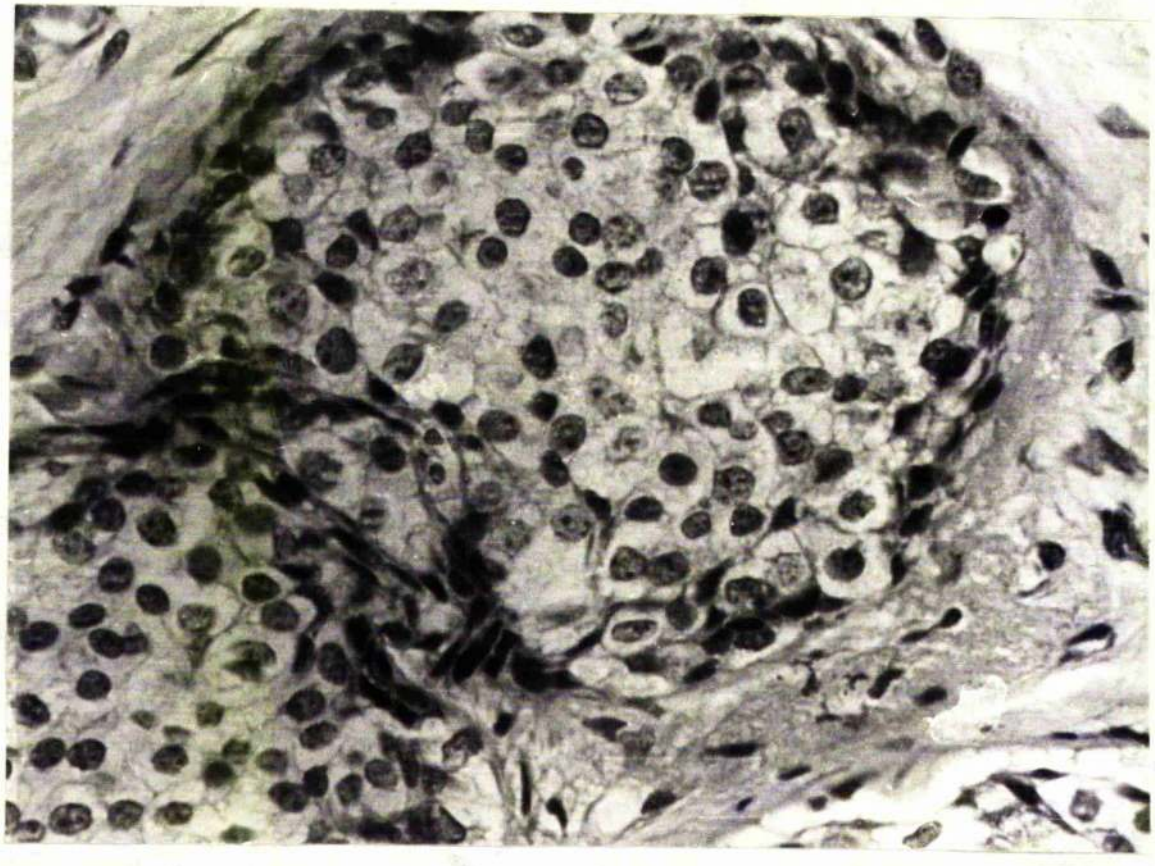


FIGURE 34: High-power view of fig. 33. The uniform vesicular malignant cells showing loss of cohesion and polarity.

Haematoxylin and eosin X 400.

PLATE 35.

Lobular Carcinoma

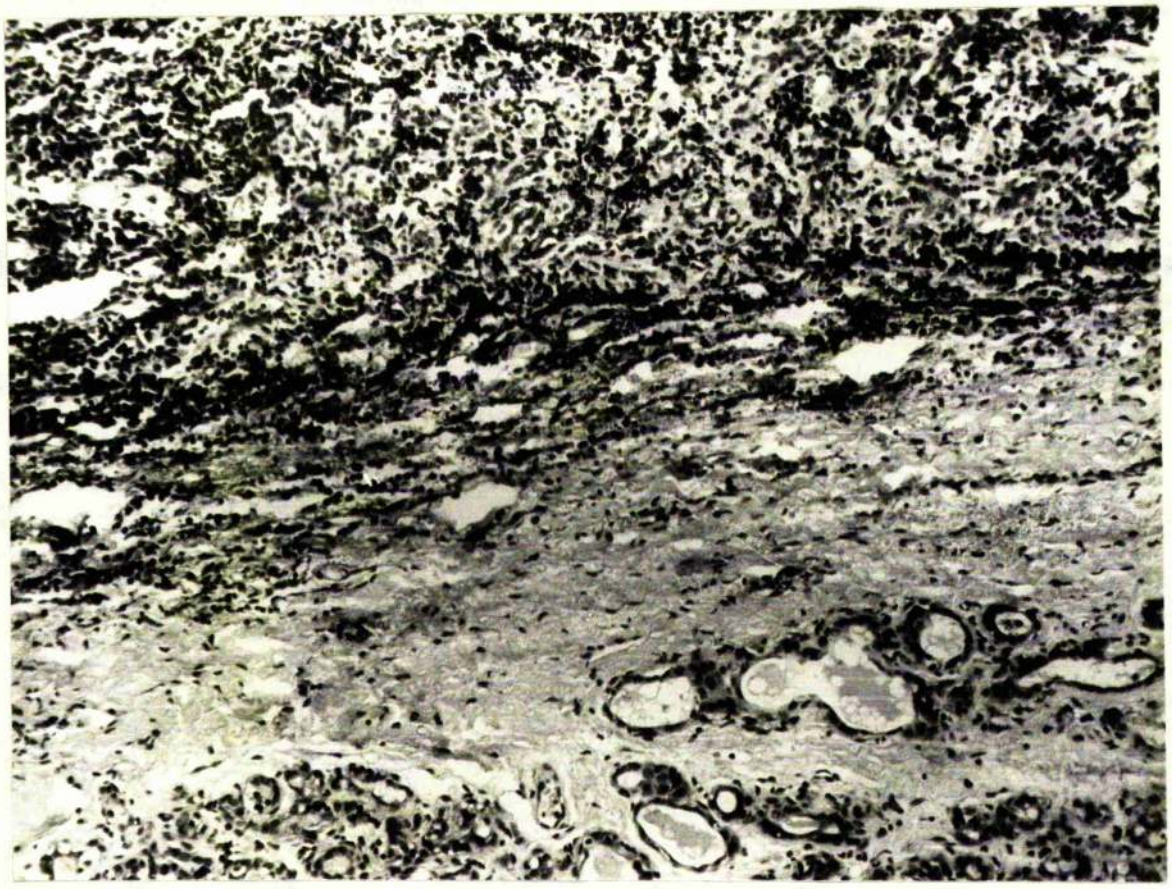


FIGURE 35: Invasive lobular carcinoma with nodular/ acinar pattern (above); observe associated fibrocystic disease, below.

PLATE 36.

Lobular carcinoma

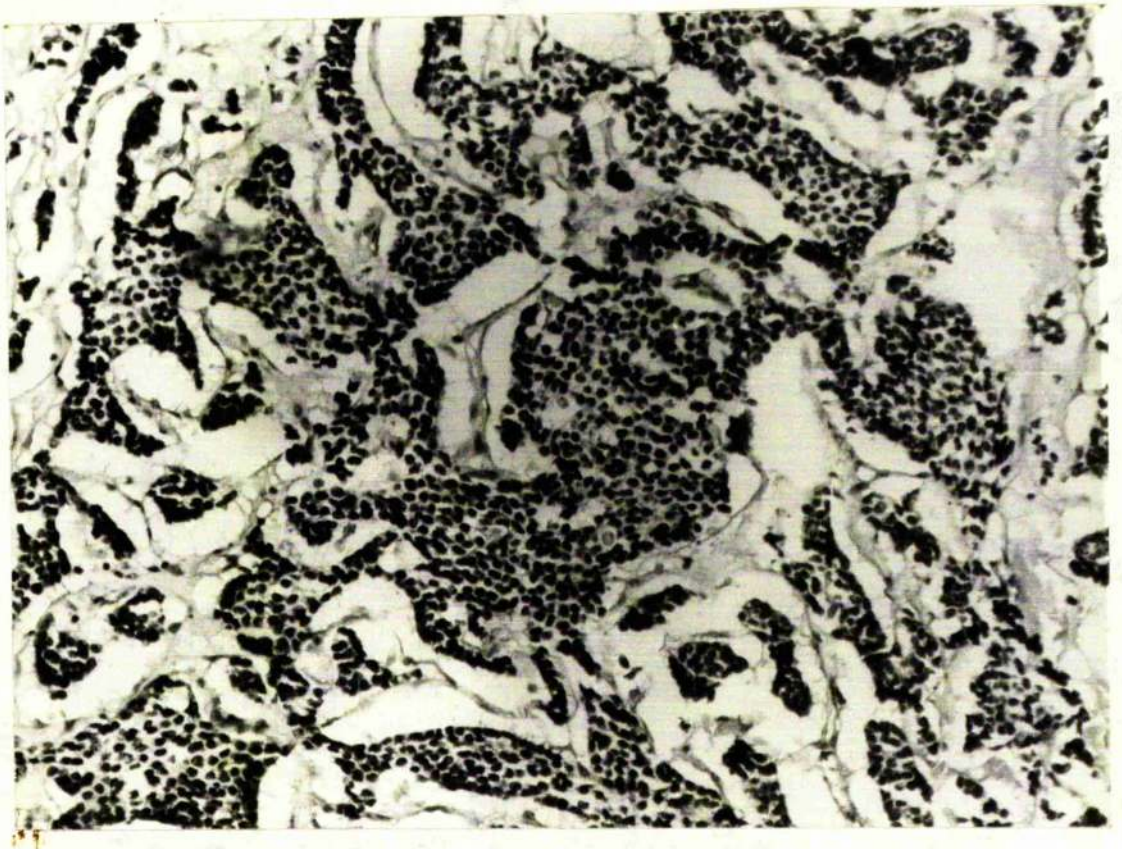


FIGURE 36: Invasive lobular carcinoma in anastomosing sheets and cords. Observe the abundant mucinous stroma.

Haematoxylin and eosin X 200.

PLATE 37.

Lobular Carcinoma

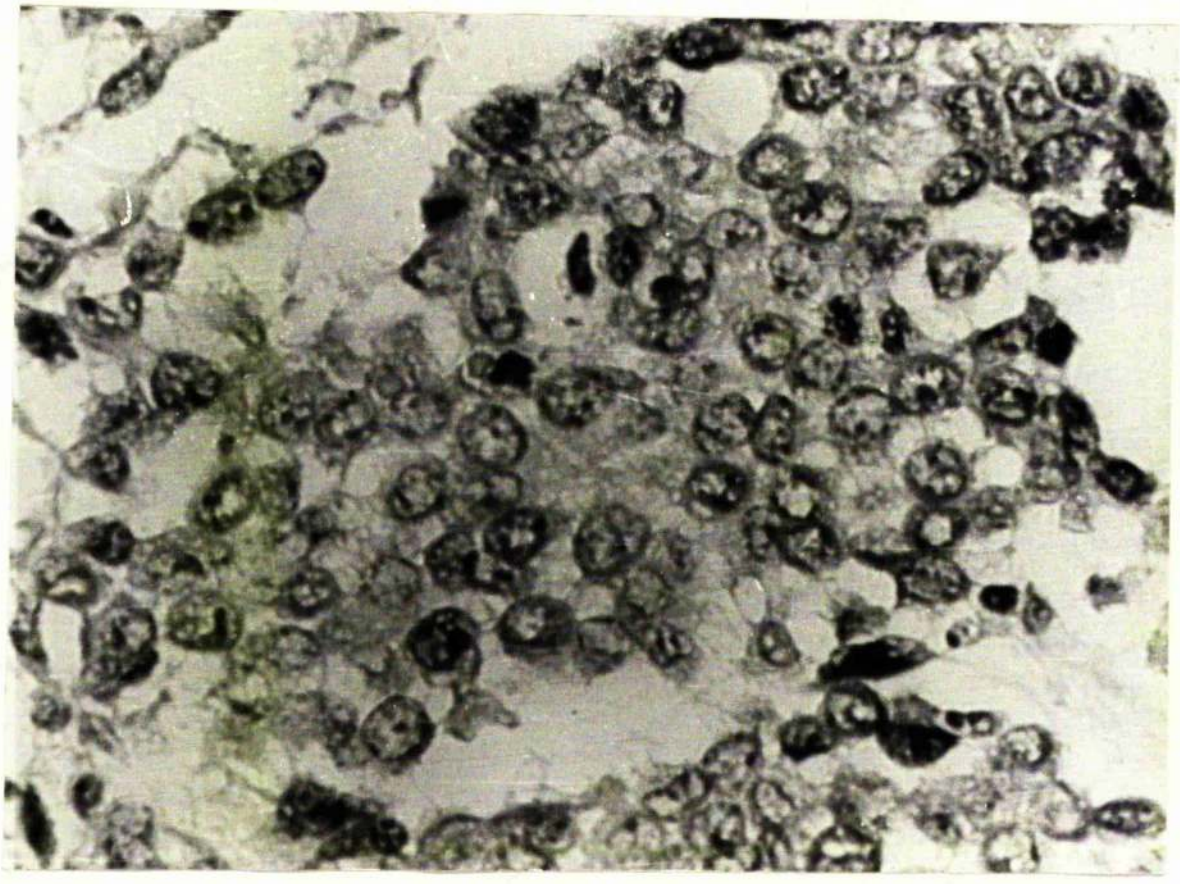


FIGURE 37: High-power view of fig. 36 showing moderate mitosis in invasive lobular carcinoma.

Haematoxylin and eosin X 400.

PLATE 38.

Lobular Carcinoma

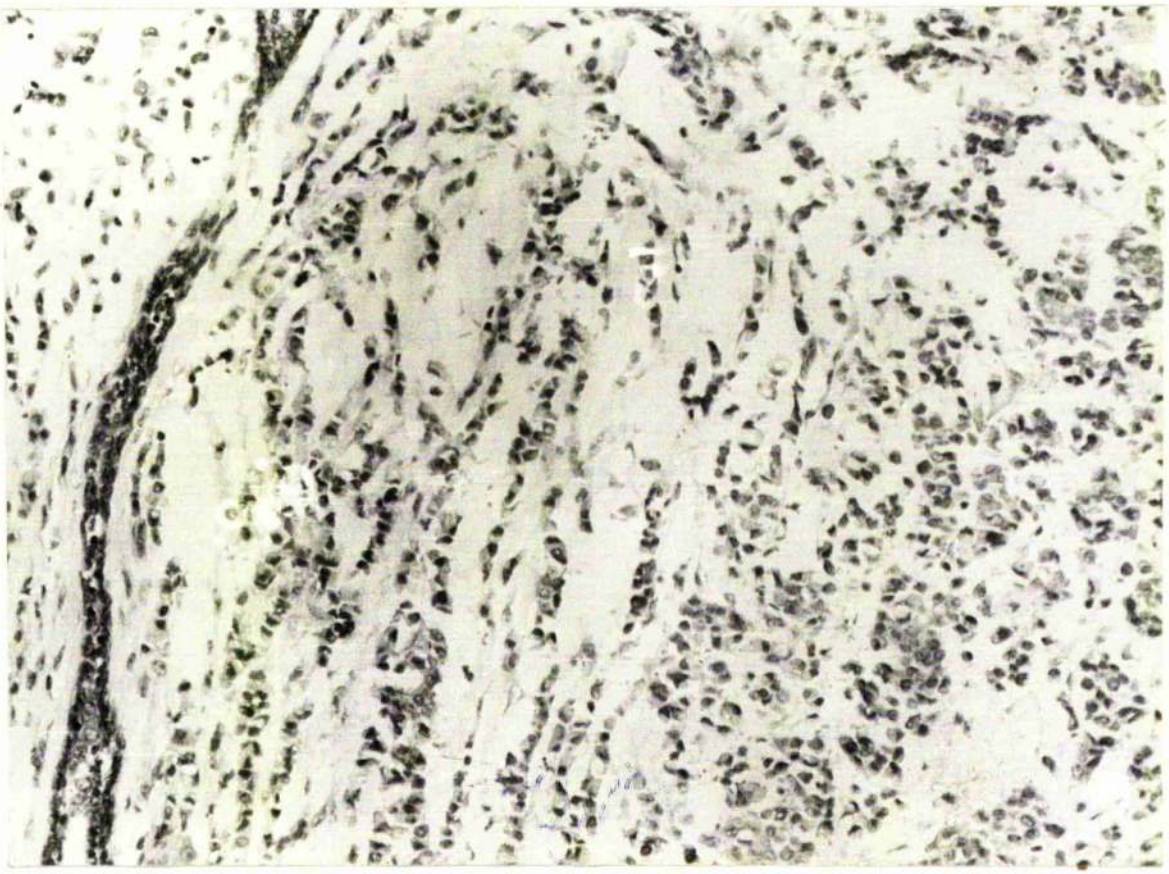


FIGURE 38: Invasive lobular carcinoma with Indian file pattern (left) in combination with medular/ acinar pattern (right).

PLATE 39.

Lobular Carcinoma

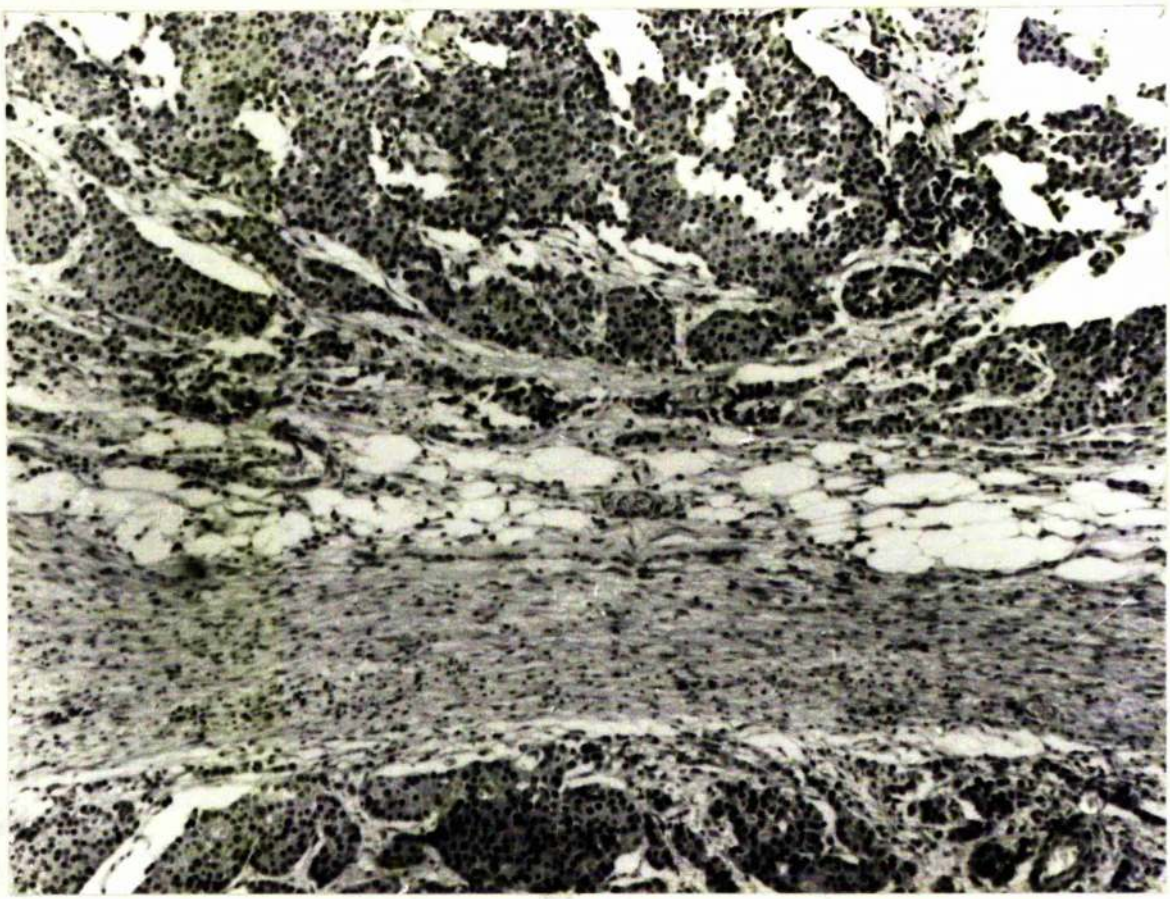


FIGURE 39: Invasive lobular carcinoma showing apocrine metaplasia in small uniform malignant cells in anastomosing sheets and nodules.

Haematoxylin and eosin X 100.

PLATE 40.

Lobular Carcinoma

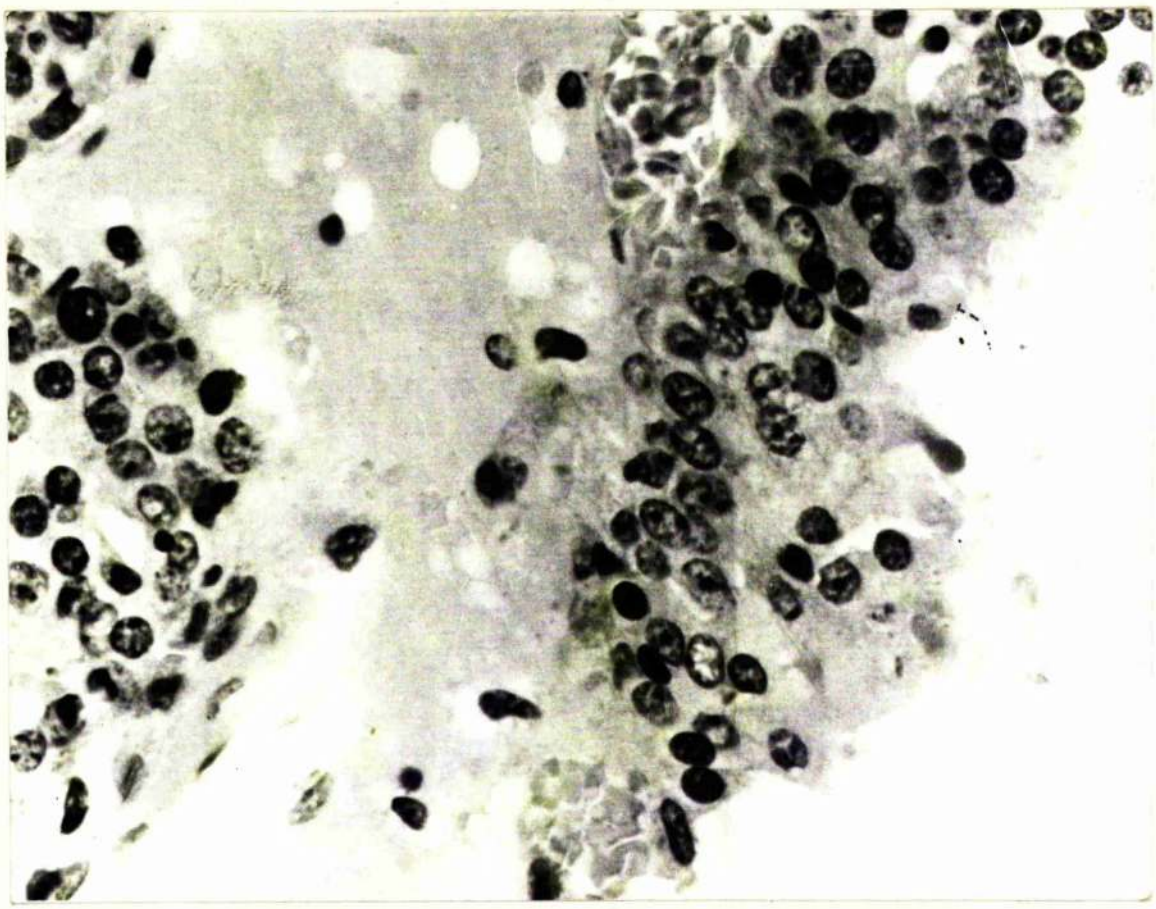


FIGURE 40: Another area of same lesion as fig. 39. Malignant cells extrude their cytoplasm into cystic cavities, as snouts projecting from the medial pole of cells (middle-right).

Haematoxylin and eosin X 440.

PLATE 41.

Lobular Carcinoma

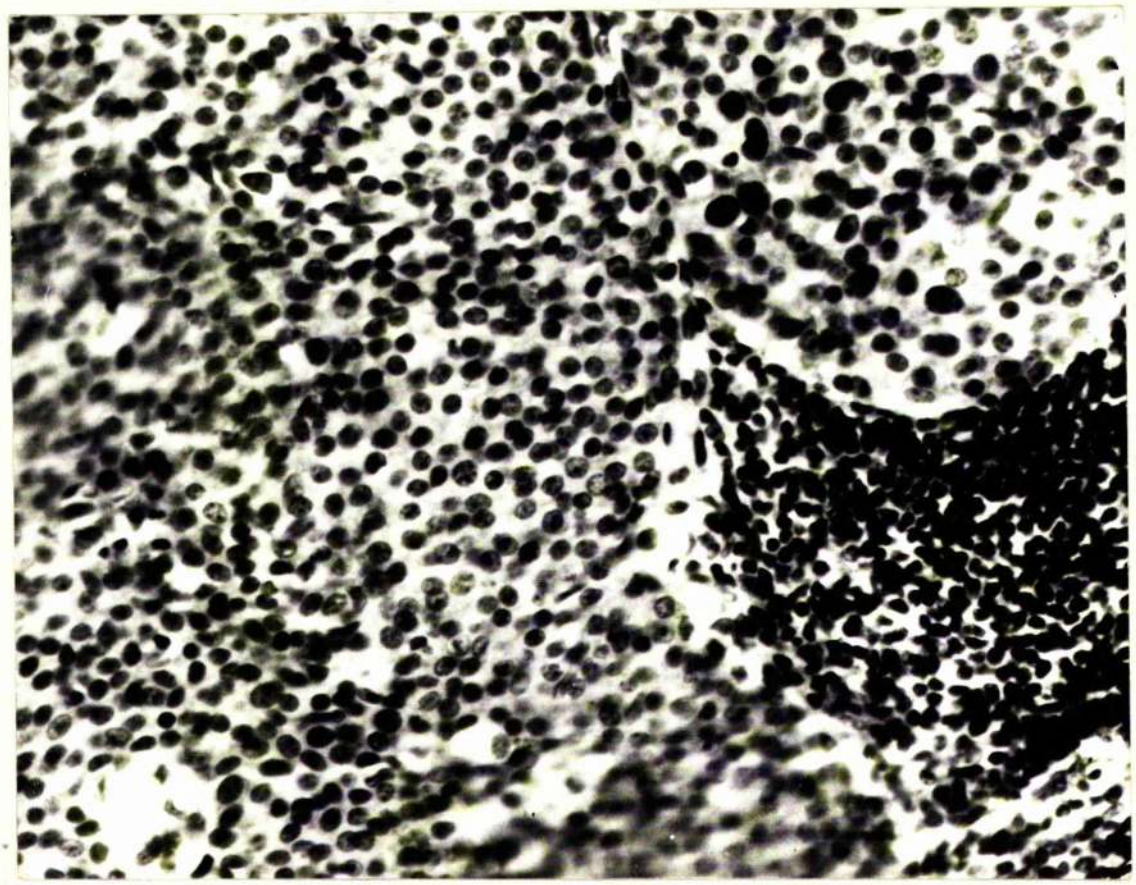


FIGURE 41: Another area of same lesion as fig. 39. The malignant cells appear as **syncytial** sheet infiltrated by abundant **lympho/ plasma cells (right).**

Haematoxylin and eosin X 200.

PLATE 42.

Lobular Carcinoma (Male 60)

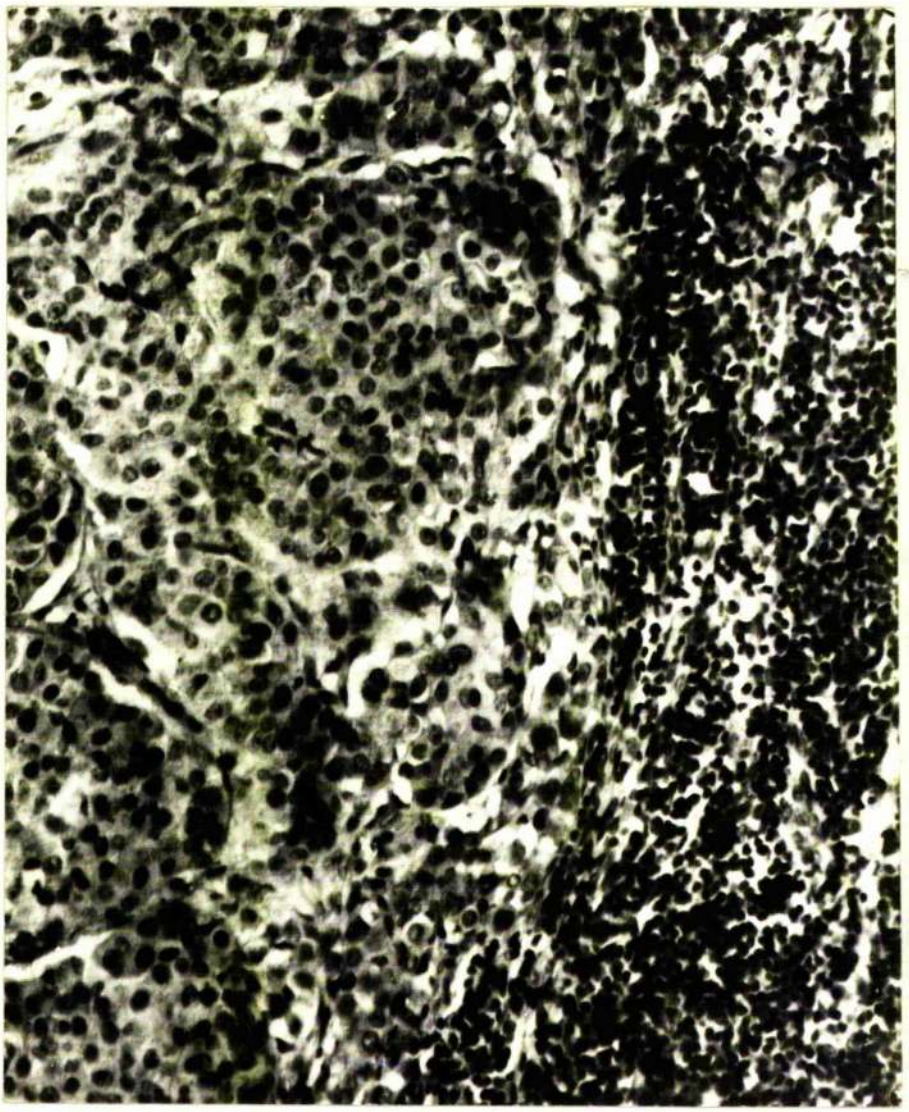


FIGURE 42: **Invasive lobular carcinoma, nodular/acinar pattern metastatic to a lymph node.**

Haematoxylin and eosin X 200.

PLATE 43.

Lobular Carcinoma (Male 60)

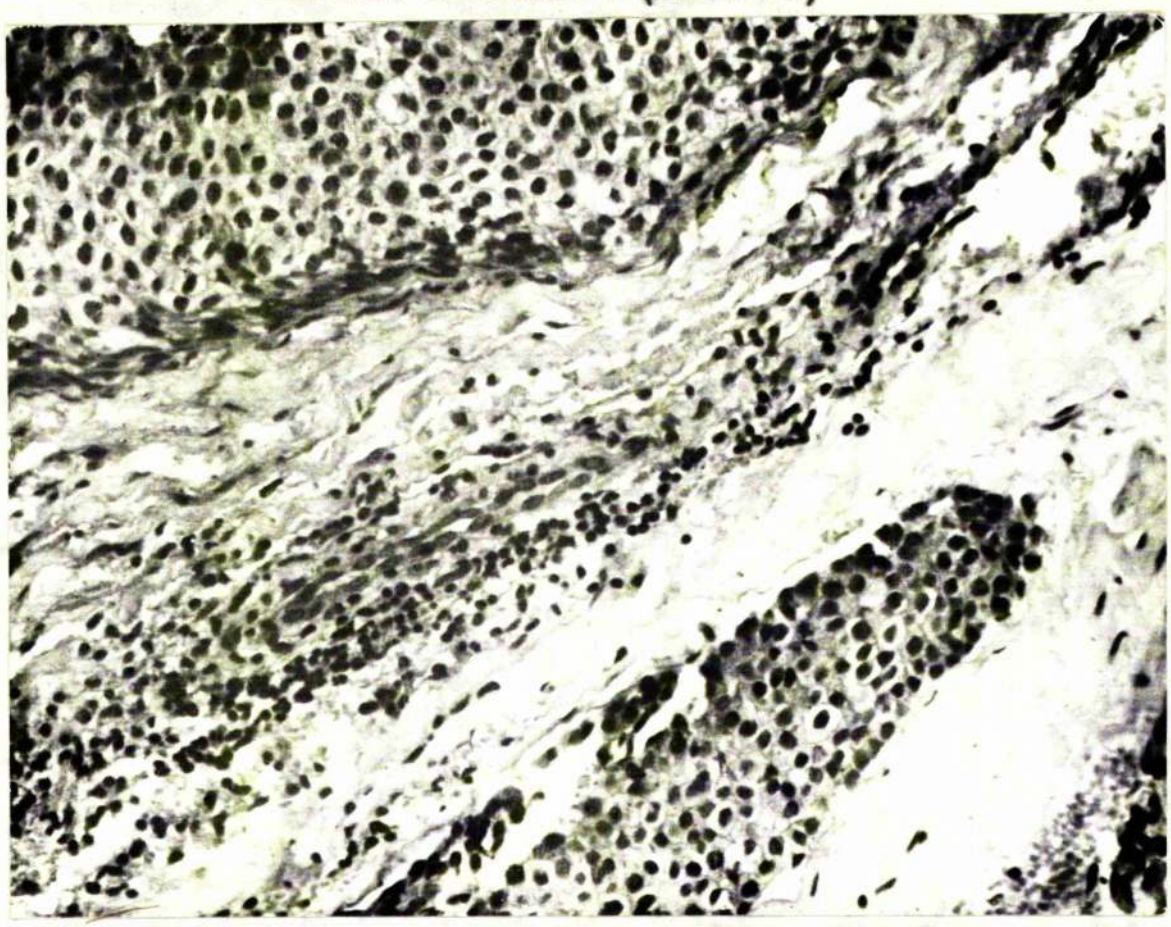


FIGURE 43: In situ lobular carcinoma associated with invasive lobular carcinoma (lesion of the 60-year old patient) described in the text.

Haematoxylin and eosin X 200.

PLATE 44.

Invasive Lobular Carcinoma (Male 60)

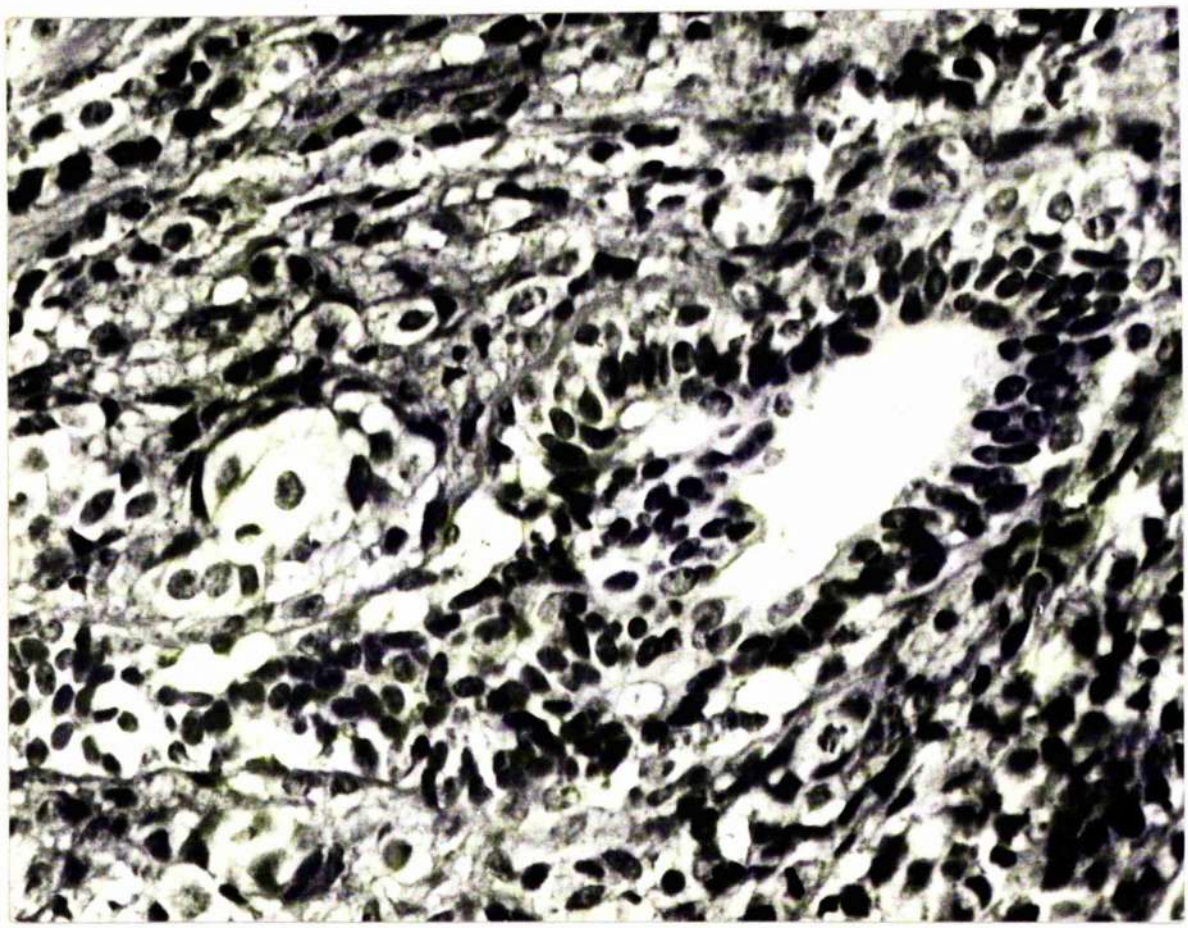


FIGURE 44: Another area of lesion as fig. 42, showing invasive lobular carcinoma, nodular/acinar pattern, surrounding a dilated duct (right).

Haematoxylin and eosin X 290.

PLATE 45.

Invasive Lobular Carcinoma (Male 60)

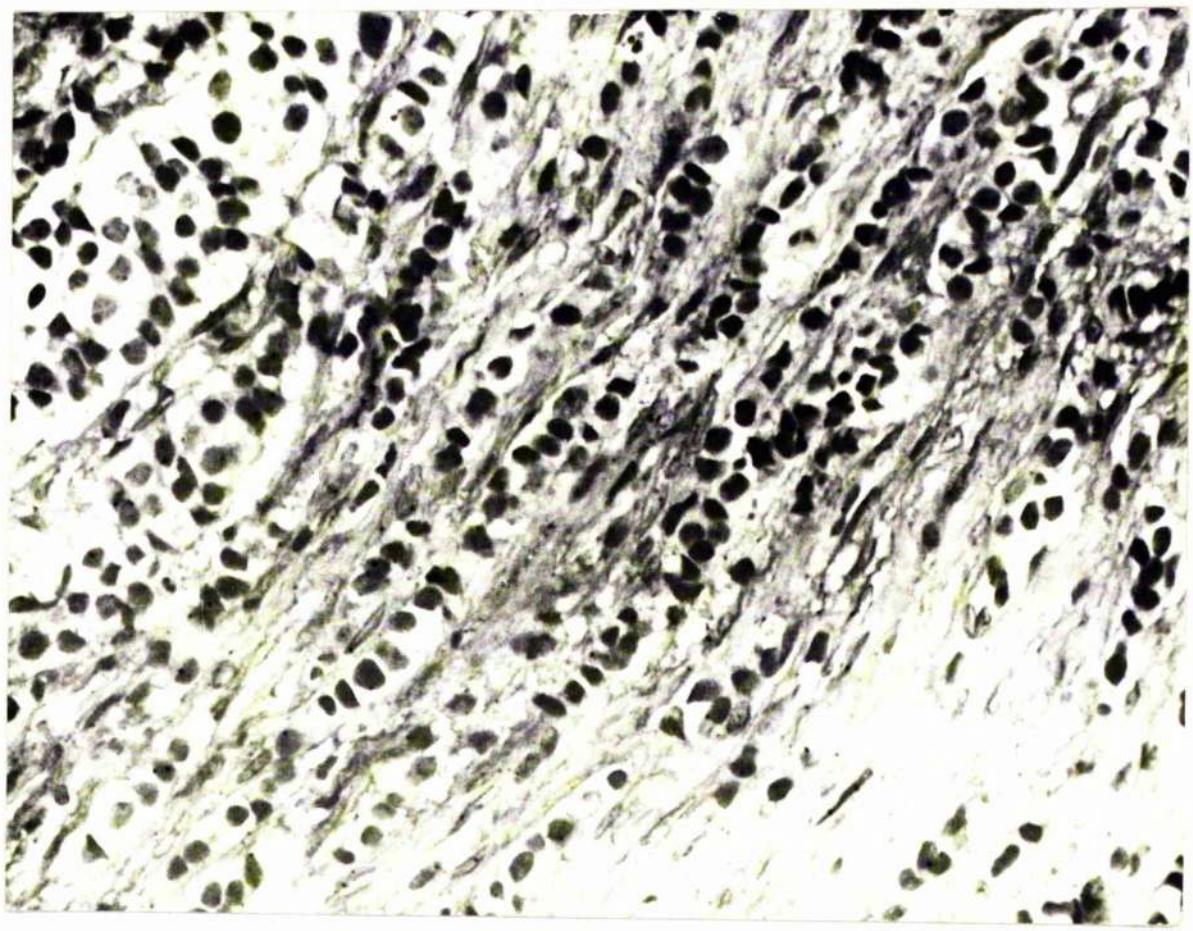


FIGURE 45: Another area of lesion as fig. 42, showing Indian file pattern (left) and nodular pattern (right) in invasive lobular carcinoma.

Haematoxylin and eosin X 290.

PLATE 46.

Invasive Lobular Carcinoma (Male 60)

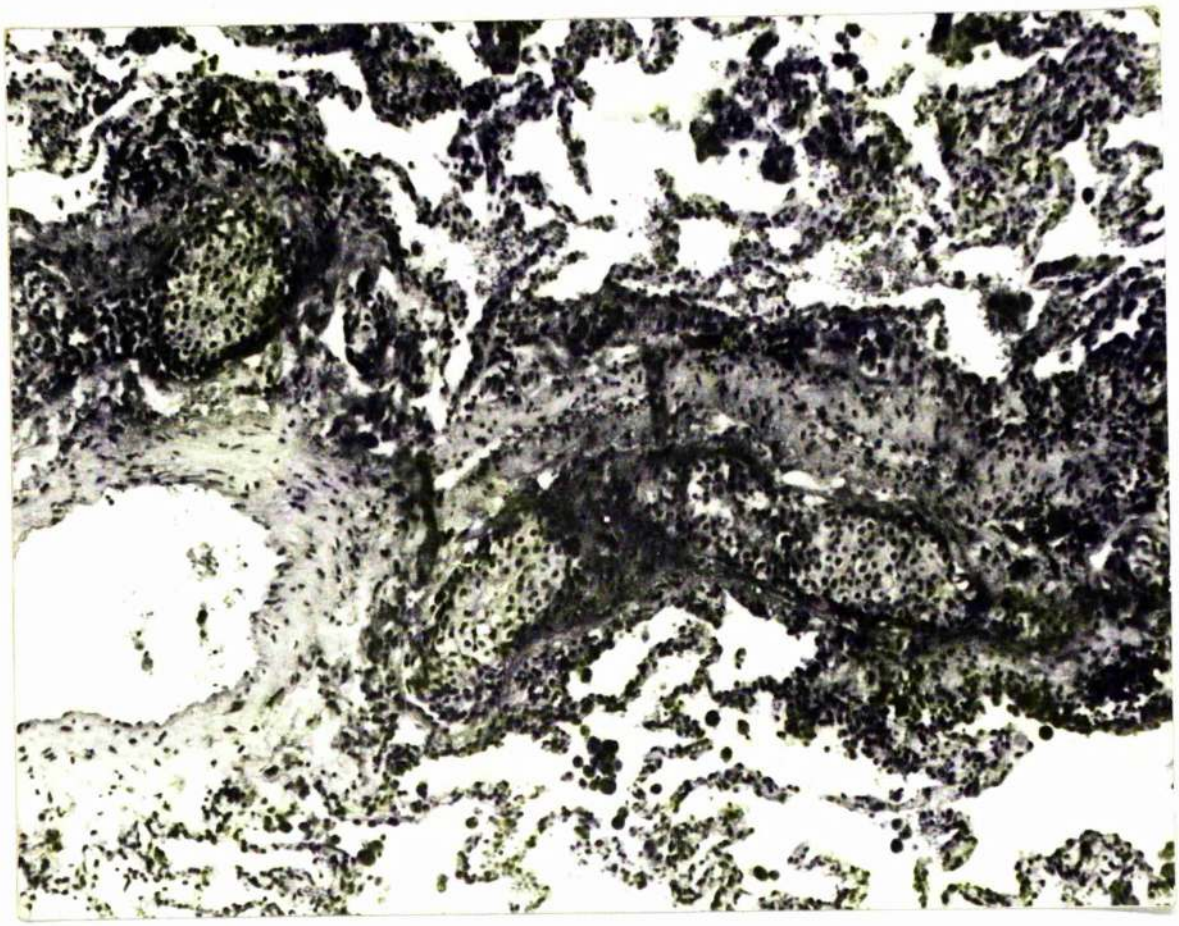


FIGURE 46: Pulmonary metastases of invasive lobular carcinoma in the 60-year old man.

Haematoxylin and eosin X 100.

PLATE 47.

Invasive Lobular Carcinoma (Male 60)

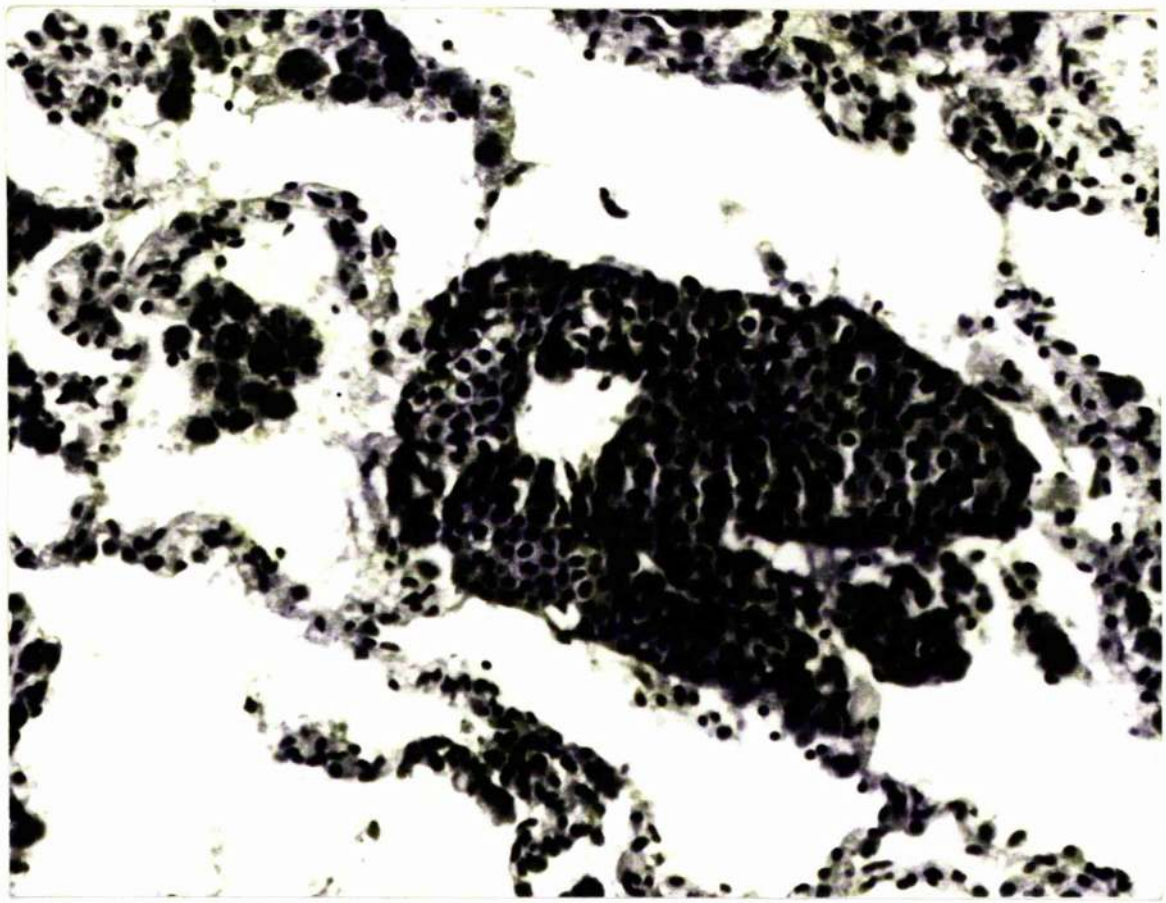


FIGURE 47: Disruption of pulmonary aveoli by metastatic invasive lobular carcinoma of the same patient as fig. 42.

Haematoxylin and eosin X 200.

PLATE 48.

Invasive Lobular Carcinoma (Male 60)

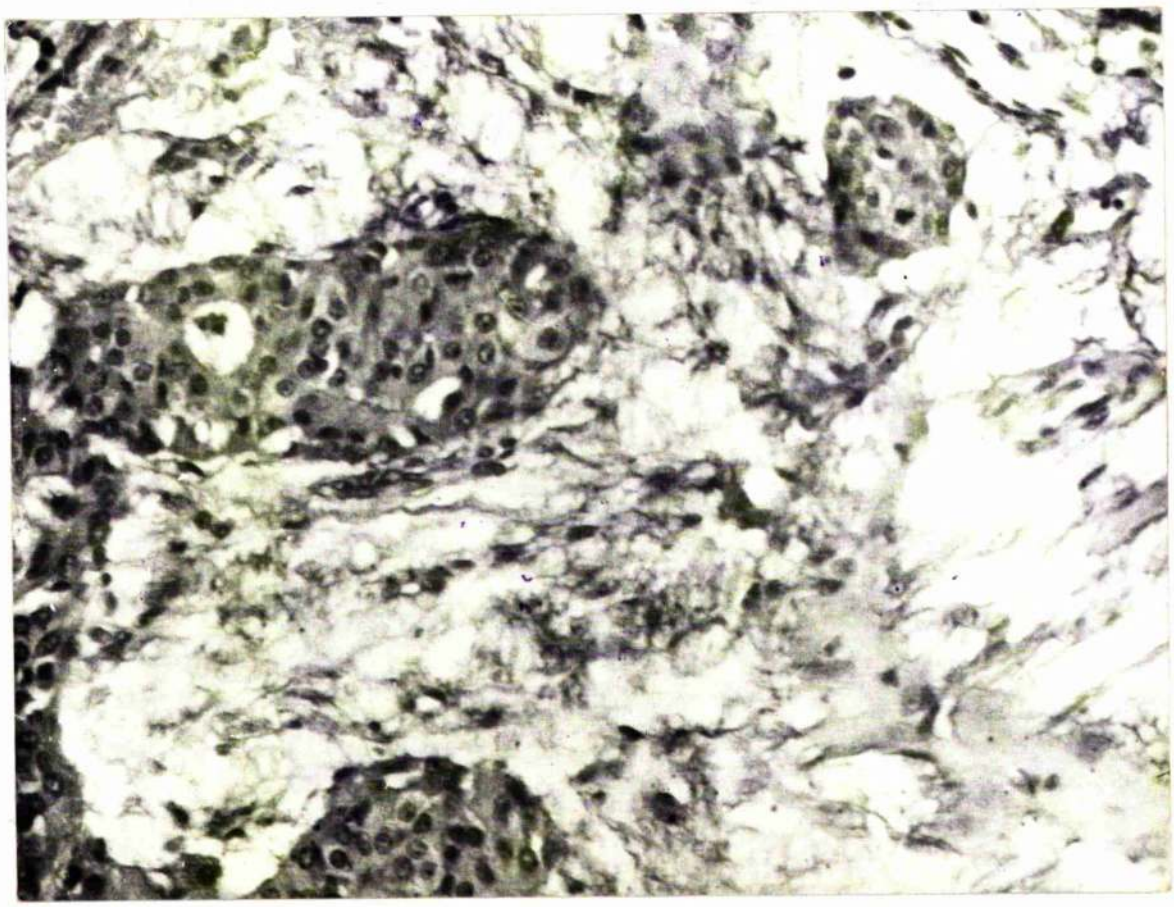


FIGURE 28: Pleural metastases of invasive lobular carcinoma of the same patient as fig. 42.

HAEMATOXYLIN and EOSIN X 200.

PLATE 49.

Medullary Carcinoma

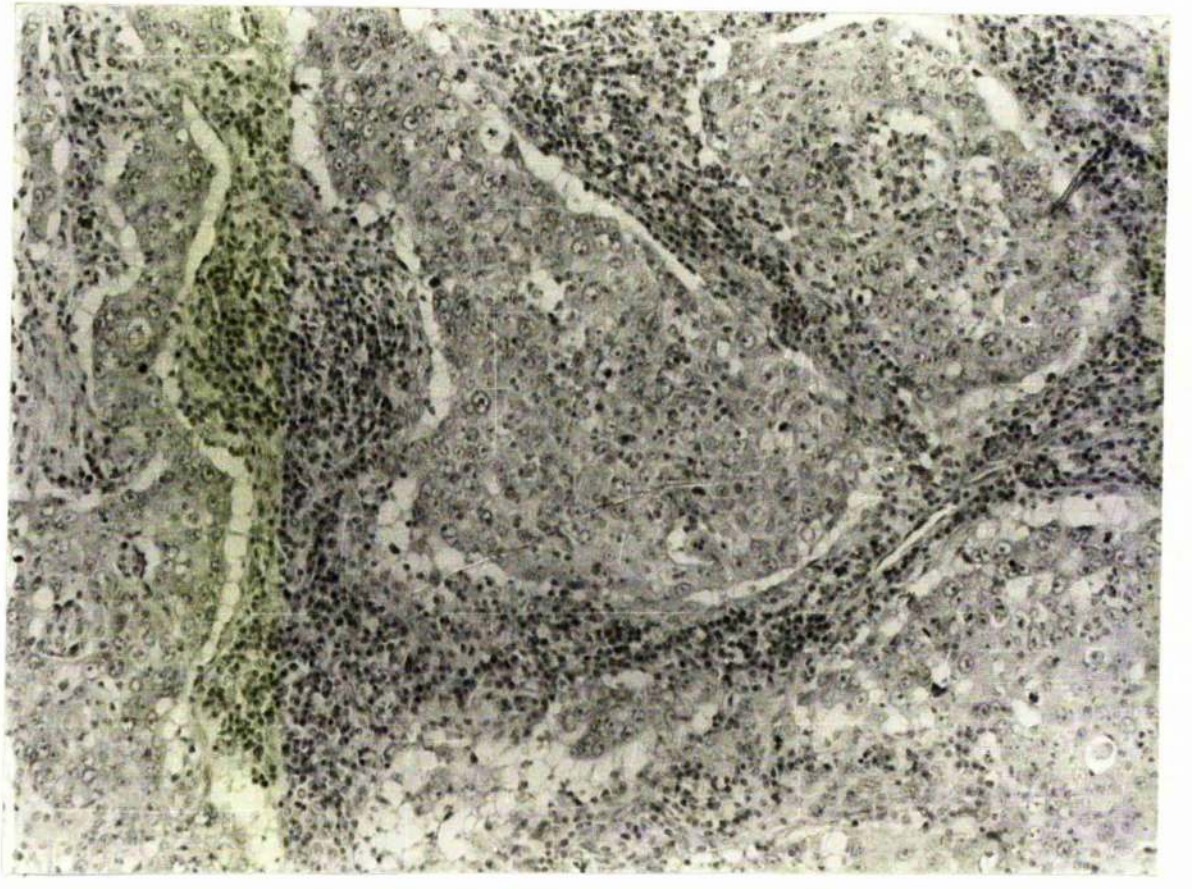


FIGURE 49: Typical syncytial medullary carcinoma **with** lympho/plasma cell infiltration.

Haematoxylin and eosin X 200.

PLATE 50.

Medullary Carcinoma

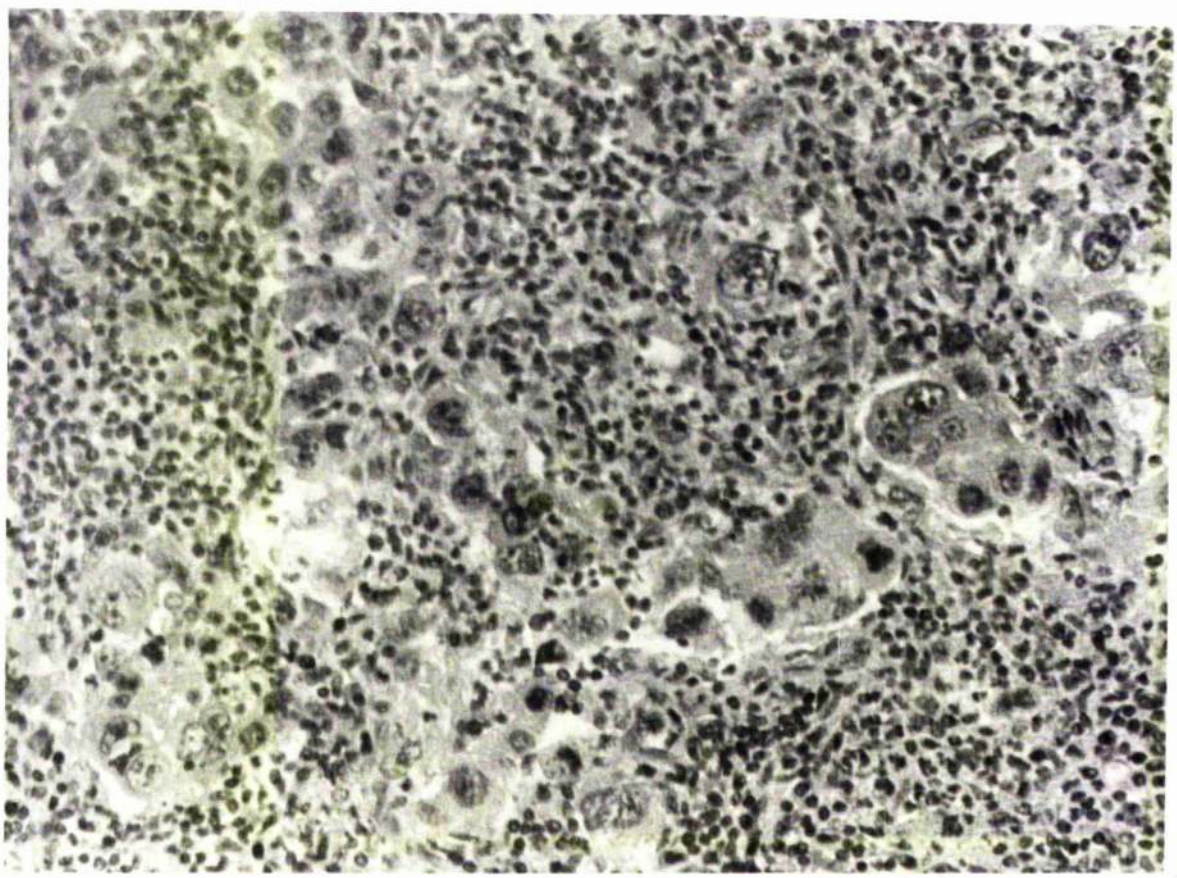


FIGURE 50: Medullary carcinoma with lympho/plasma cell infiltration. Lymphocytes by process of emperipolesis enter the cytoplasm of some dissociated malignant cells.

Haematoxylin and eosin X 290.

PLATE 51.

Medullary Carcinoma

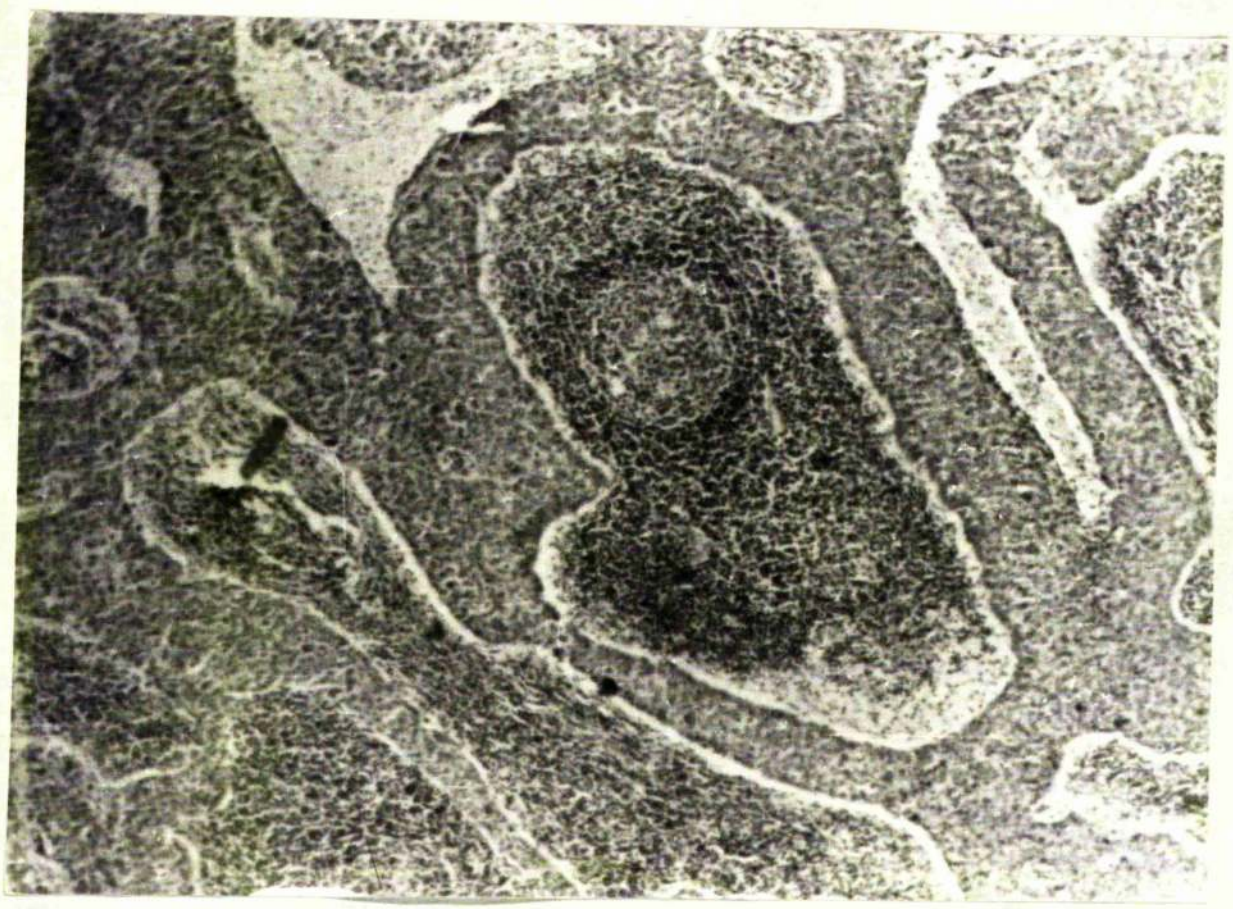


FIGURE 51: Medullary carcinoma with lympho/plasma cell infiltration showing lymphoid follicle with germinal centre.

Haematoxylin and eosin X 200.

PLATE 52.

Medullary Carcinoma

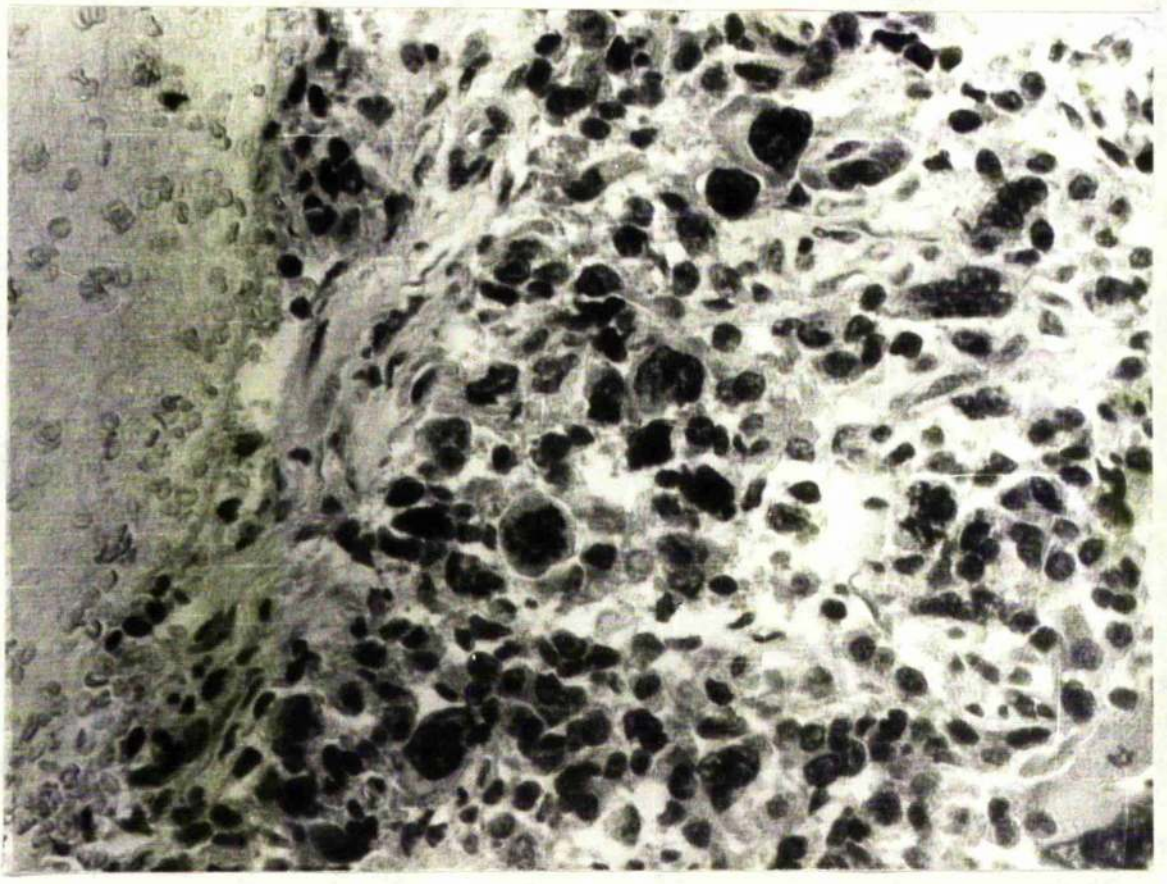


FIGURE 52: Medullary carcinoma composed mainly of malignant giant cells. Observe bizarre mitosis.

Haematoxylin and oesin X 400.

PLATE 53.

Medullary Carcinoma

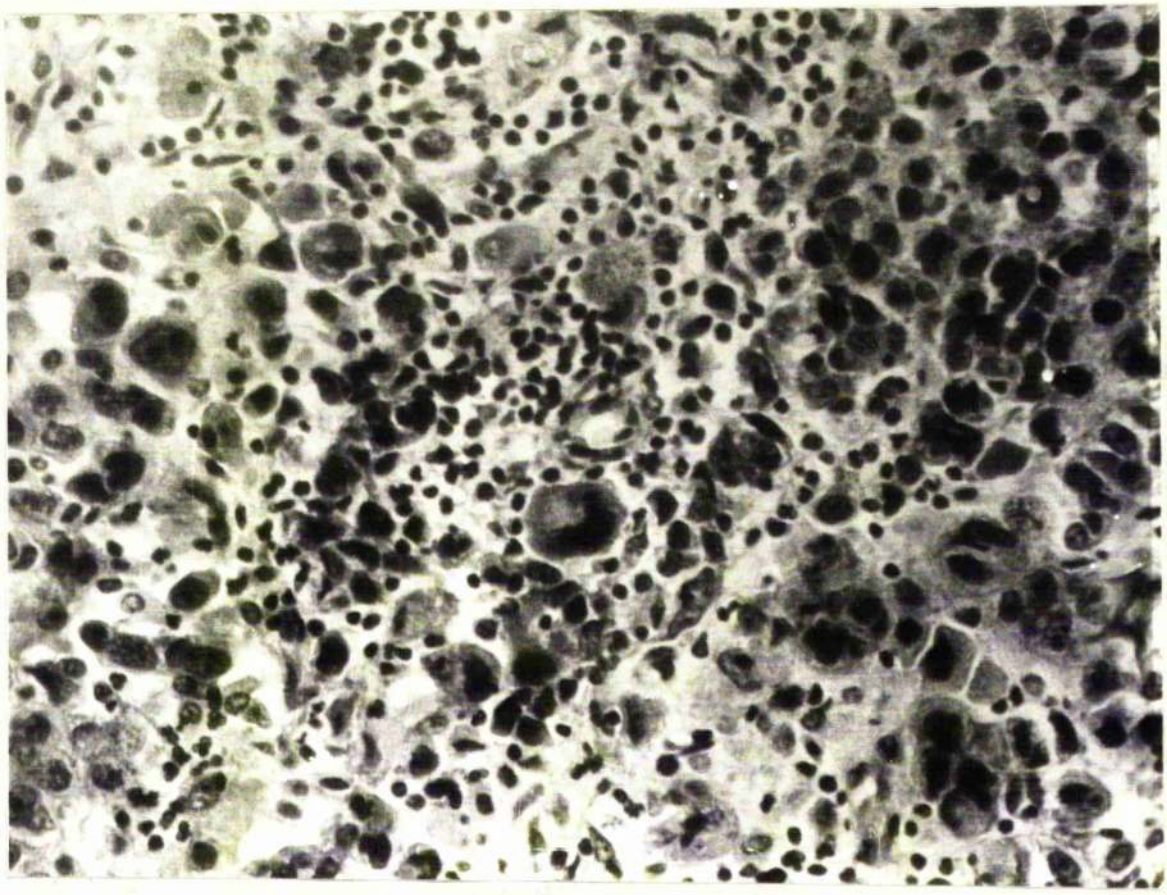


FIGURE 53: Medullary carcinoma composed mainly of malignant giant cells. Observe host lymphocytes attacking the malignant cells.

Haematoxylin and eosin X 400.

PLATE 54.

Medullary Carcinoma

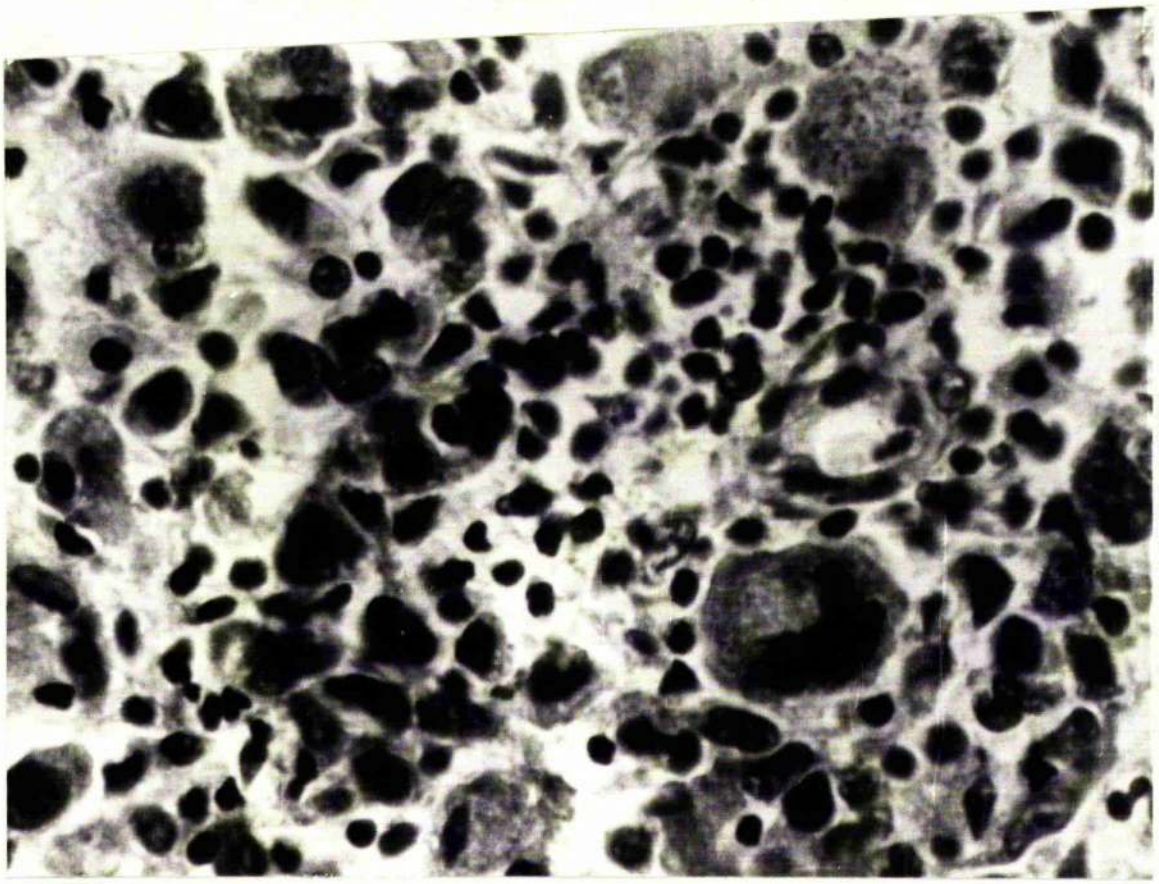


FIGURE 54: High-power view of fig. 53 illustrating the phenomenon of emperipolesis by host lymphocytes.

Haematoxylin and eosin X 900.

PLATE 55.

Medullary Carcinoma

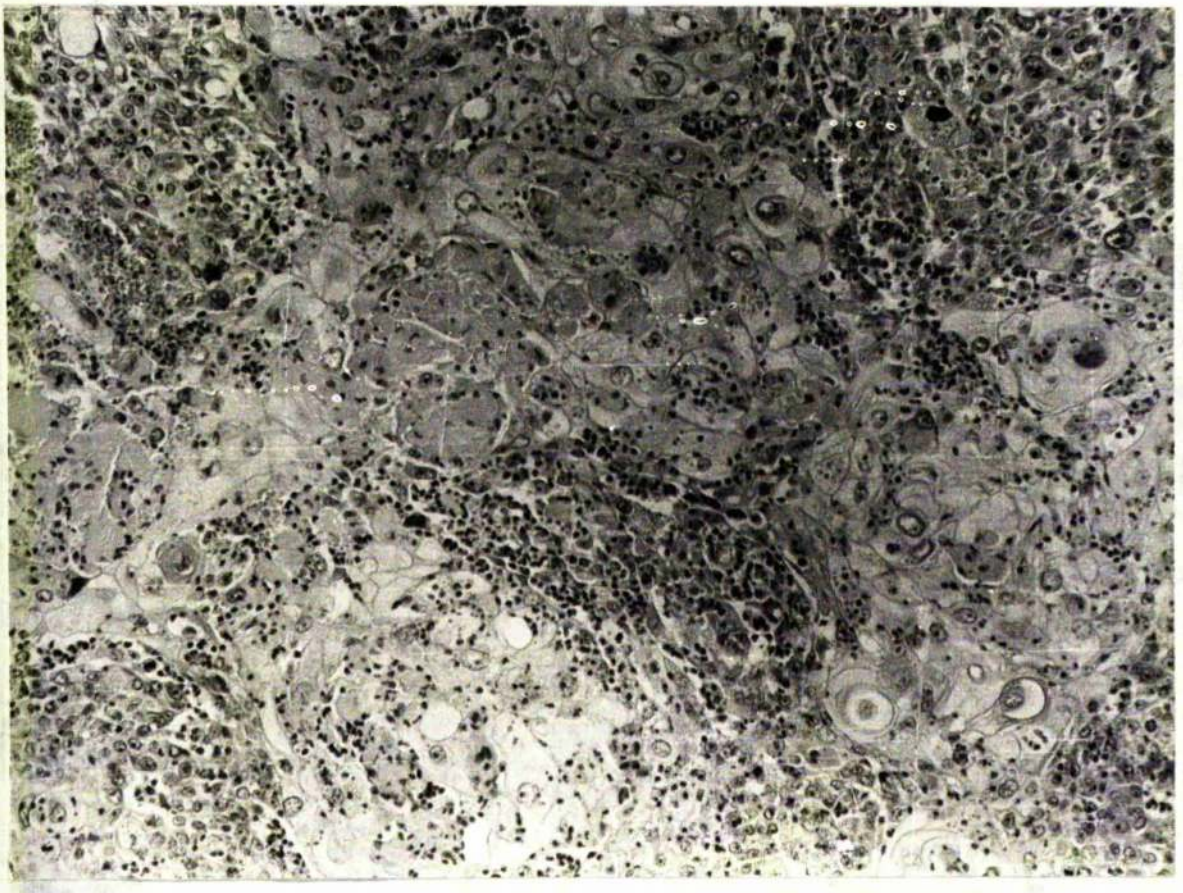


FIGURE 55: Medullary carcinoma with polymorph infiltration. Observed maligaant cells with ballooning and hyaline degeneration.

Haematoxylin and eosin X 200.

PLATE 56.

Medullary Carcinoma

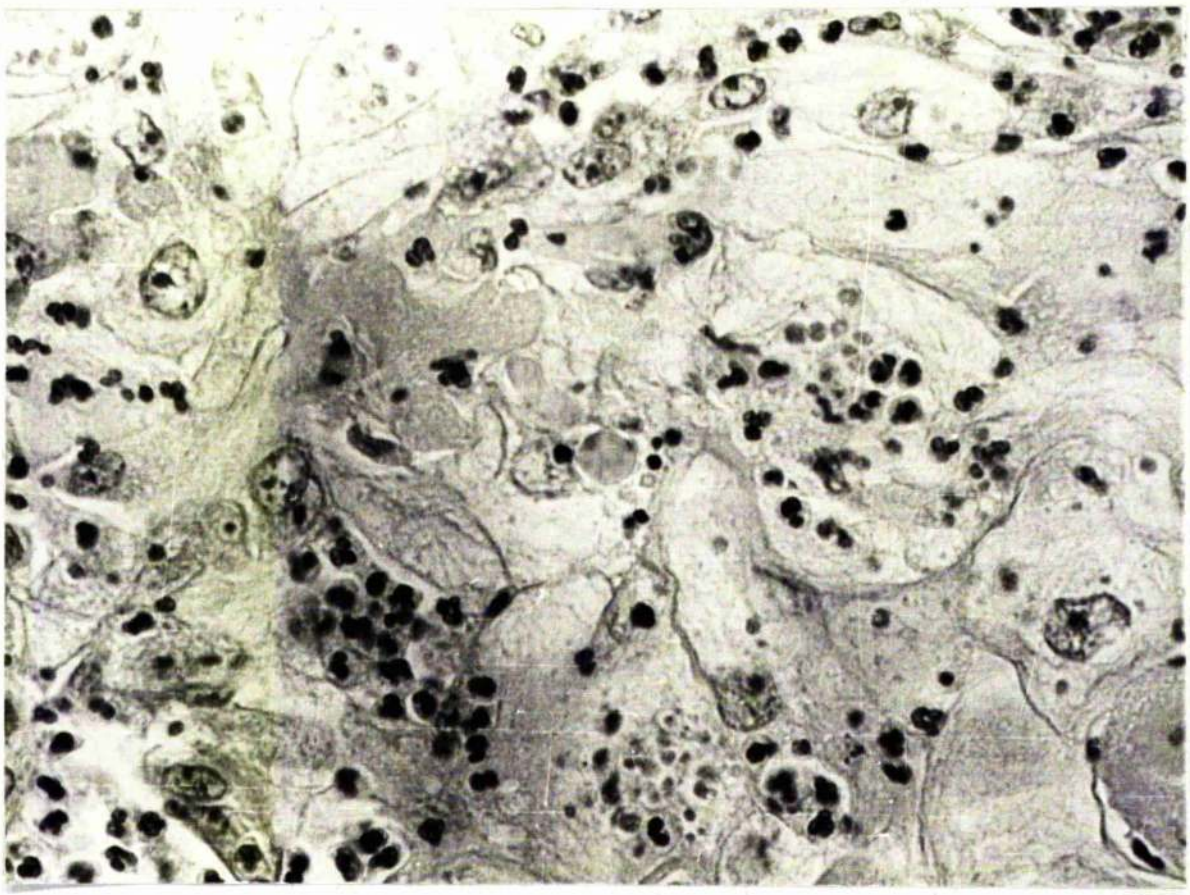


FIGURE 56: High-power view of fig. 55; observe polymorphs in cytoplasm of ballooned malignant cells with distinct borders.

Haematoxylin and eosin X 290.

PLATE 57.

Medullary Carcinoma

FIGURE 57: Medullary carcinoma with polymorph infiltration showing an area of liquefaction necrosis.

Haematoxylin and eosin X 200.

PLATE 58.

Medullary Carcinoma

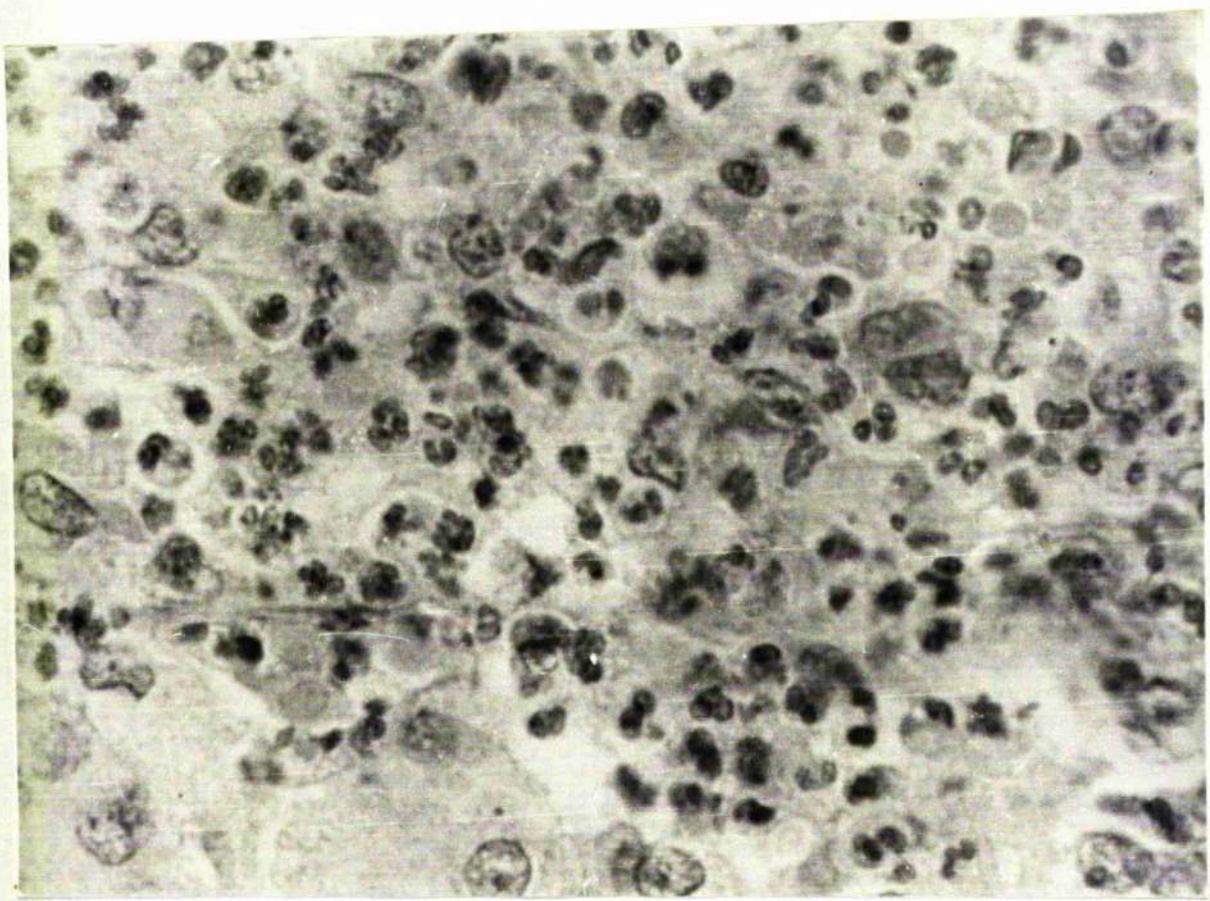


FIGURE 58: High-power view of an area as fig. 57 showing teeming polymorphs, attacking tumour cells.

Haematoxylin and eosin X 290.

PLATE 59.

Medullary Carcinoma

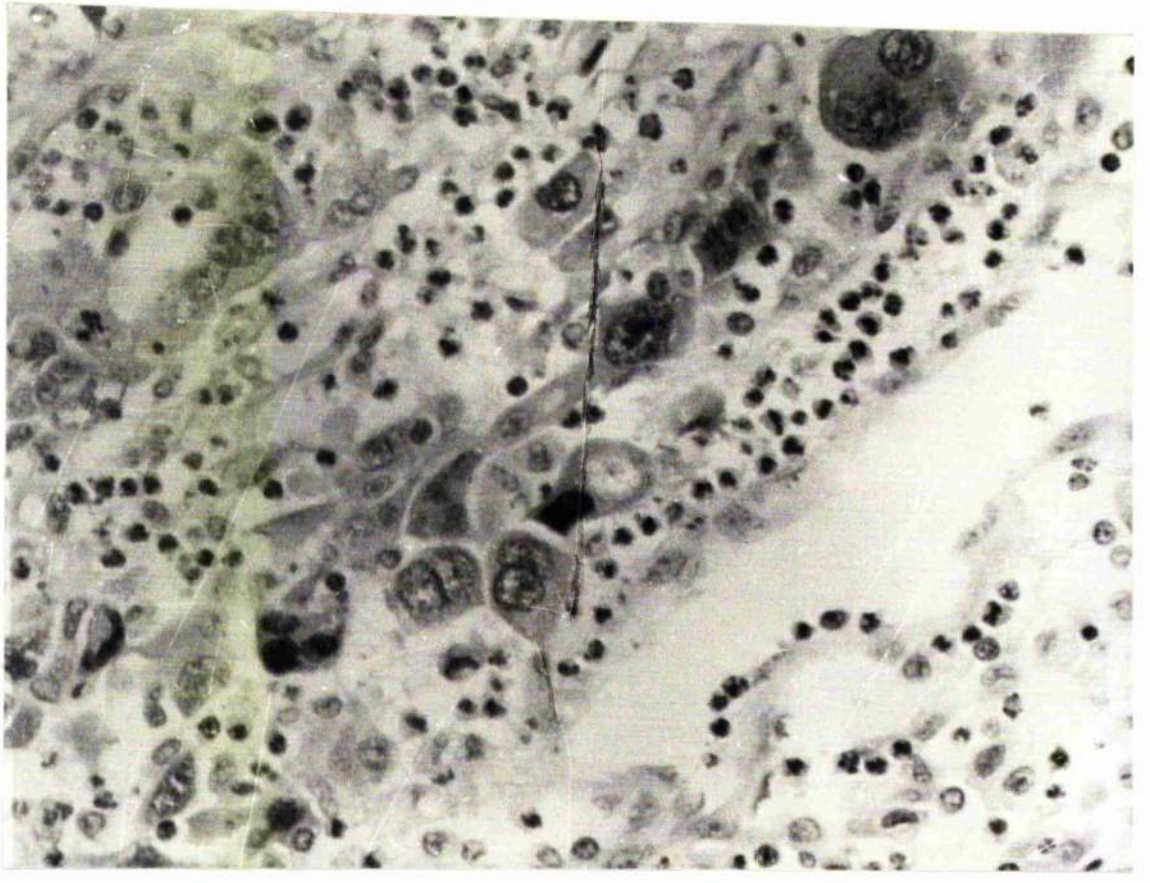


FIGURE 59: High-power view as fig. 57. Most malignant cells are undergoing liquefaction necrosis.

Haematoxylin and eosin X 290.

PLATE 60.

. Medullary Carcinoma

FIGURE 60: **Medullary carcinoma with polymorph infiltration. Observed oesinophilic coagulum from lysed malignant cells surrounded by viable malignant cells.**

Haematoxylin and eosin X 290.

PLATE 61.

Medullary Carcinoma

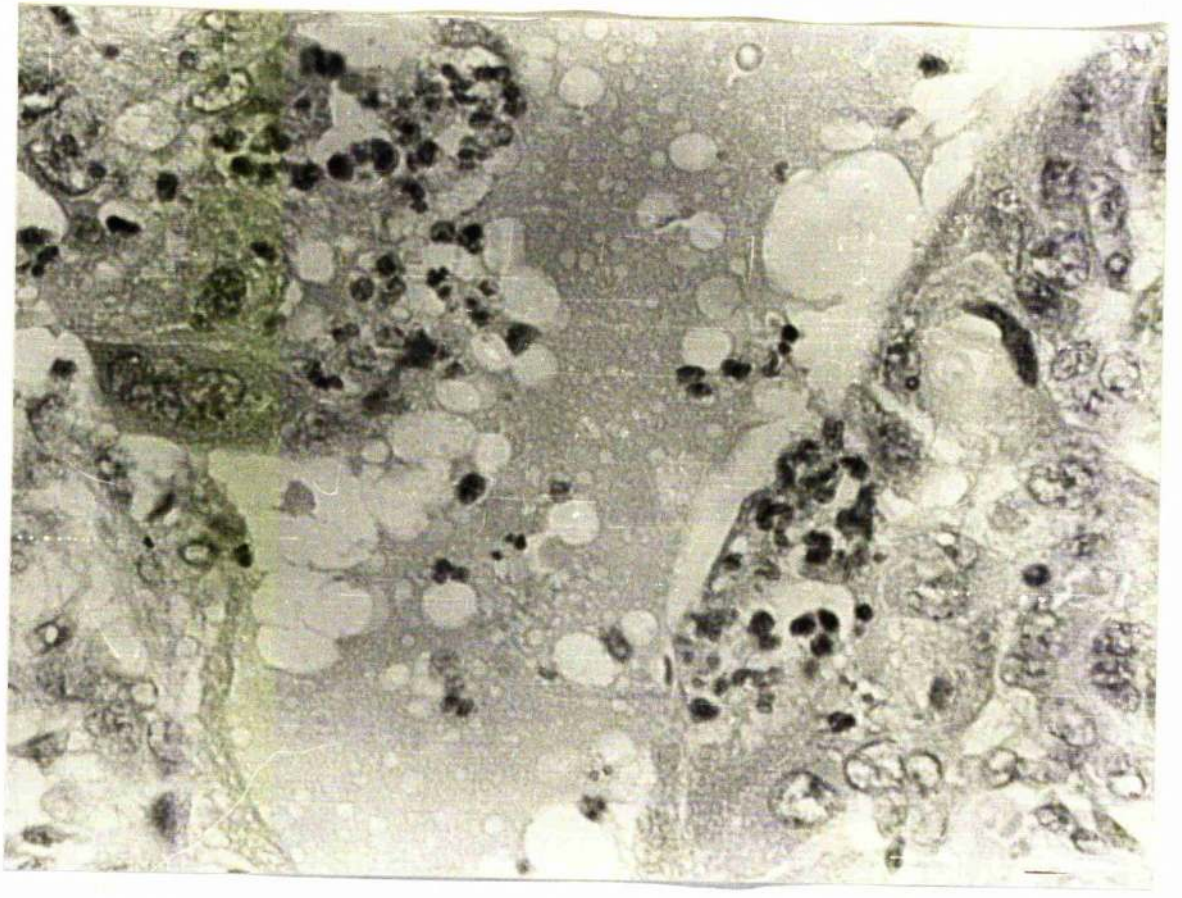


FIGURE 61: Medullary carcinoma with polymorph infiltration. Observe coalescence of smaller cysts to larger cyst containing eosinophilic coagulum.

Haematoxylin and eosin X 290.

PLATE 62.

Medullary Carcinoma

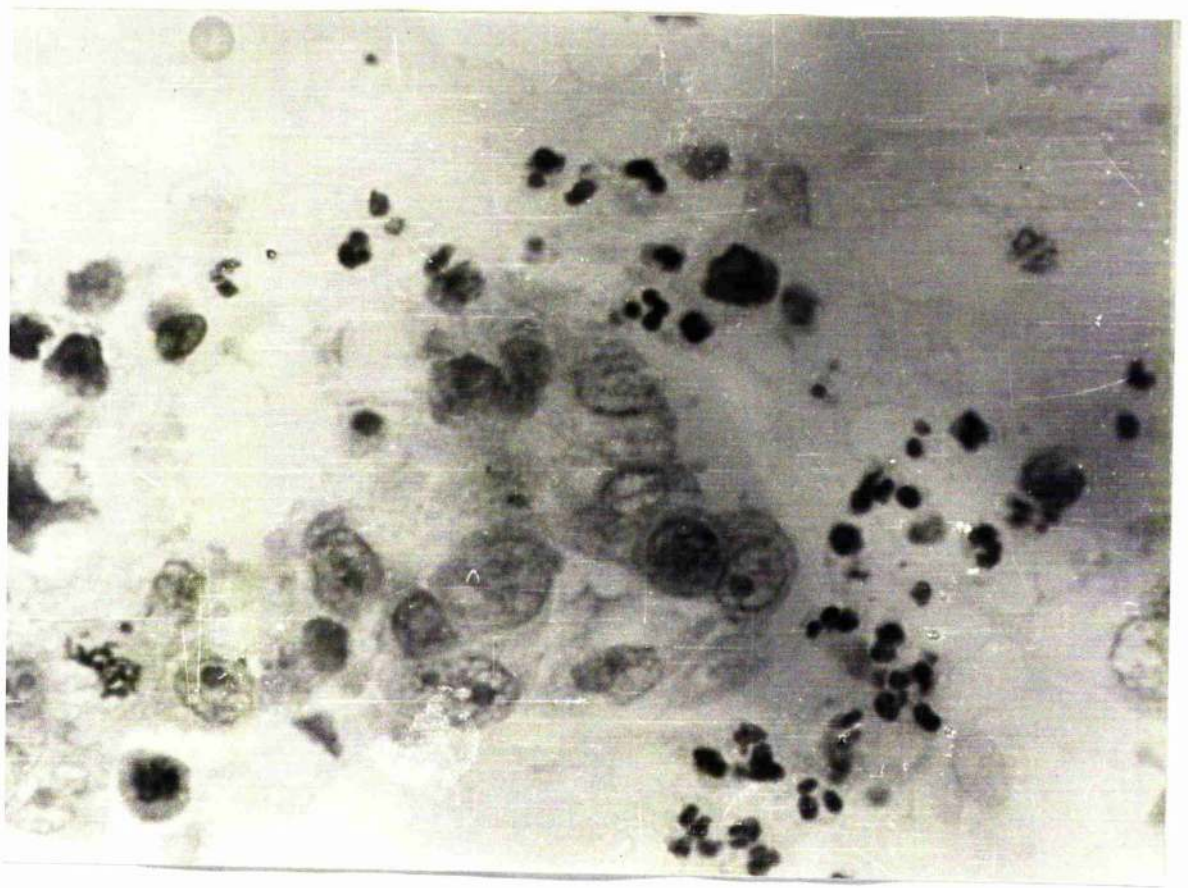


FIGURE 62: Medullary carcinoma with polymorph infiltration. Observe nest of malignant cells floating in coagulum and fenced by polymorphs.

Haematoxylin and eosin X 290.

PLATE 63.

Medullary Carcinoma

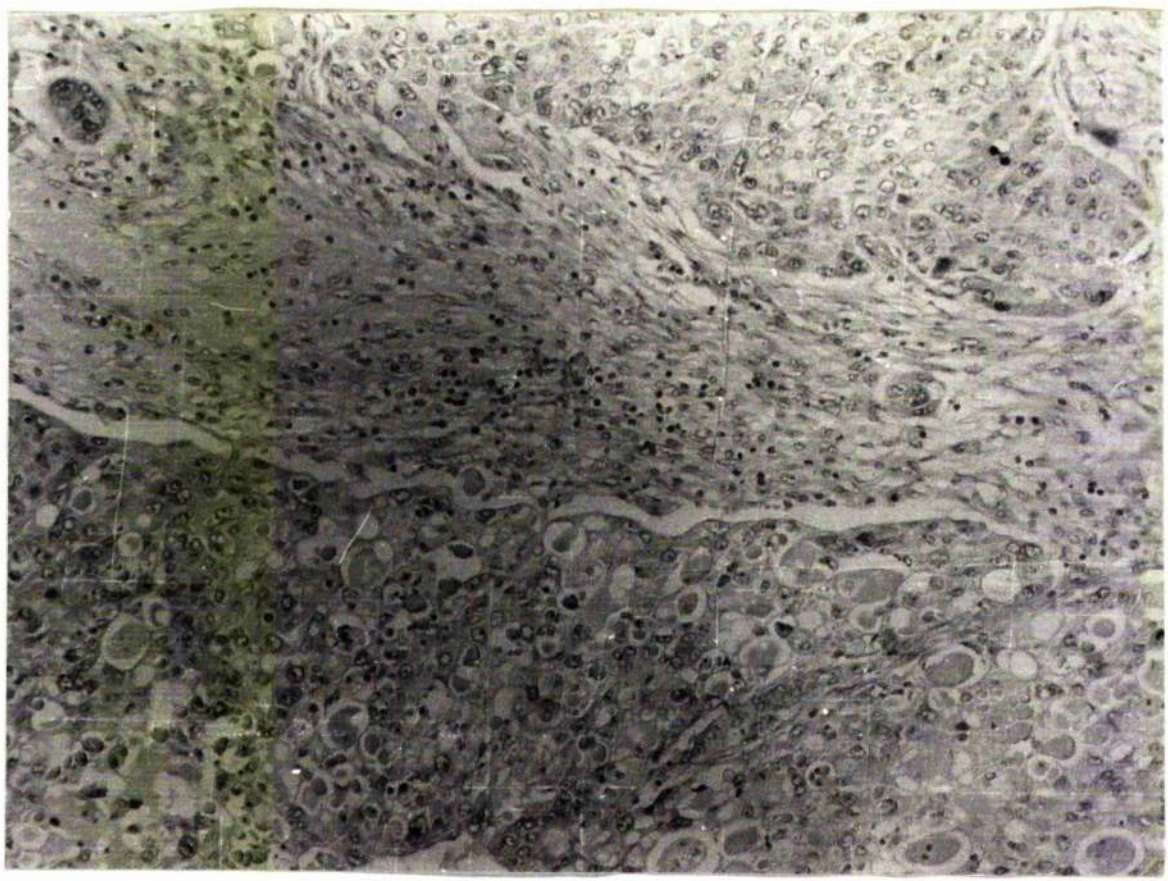


FIGURE 63: Medullary carcinoma with polymorph infiltration. Observe granulation tissue replacing the eosinophilic coagulum.

Haematoxylin and eosin X 200.

PLATE 64.

. Medullary Carcinoma

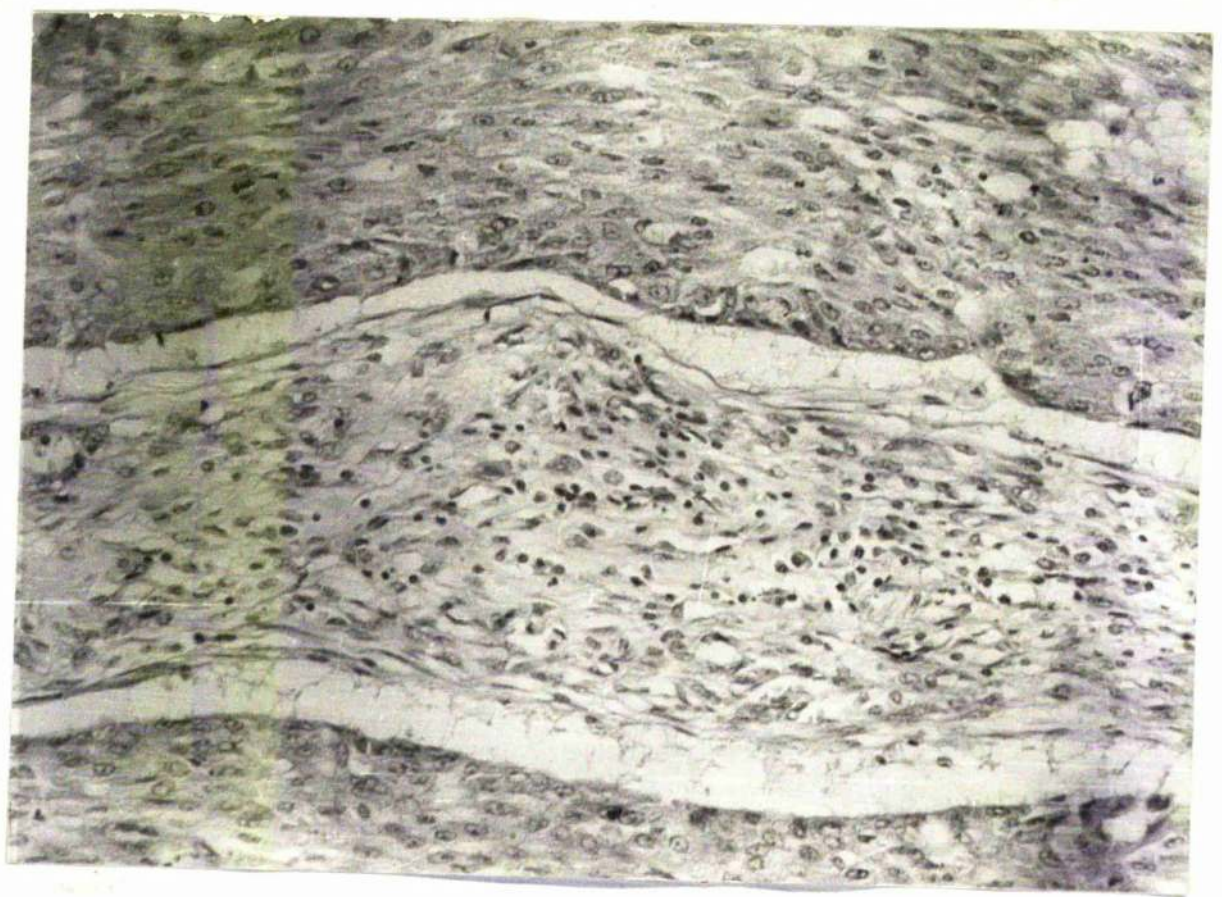


FIGURE 64: Medullary carcinoma with polymorph infiltration. Observe centfally placed matured fibrous tissues surrounded by viable malignant cells.

Haematoxylin and eosin X 290.

PLATE 65.

Medullary Carcinoma

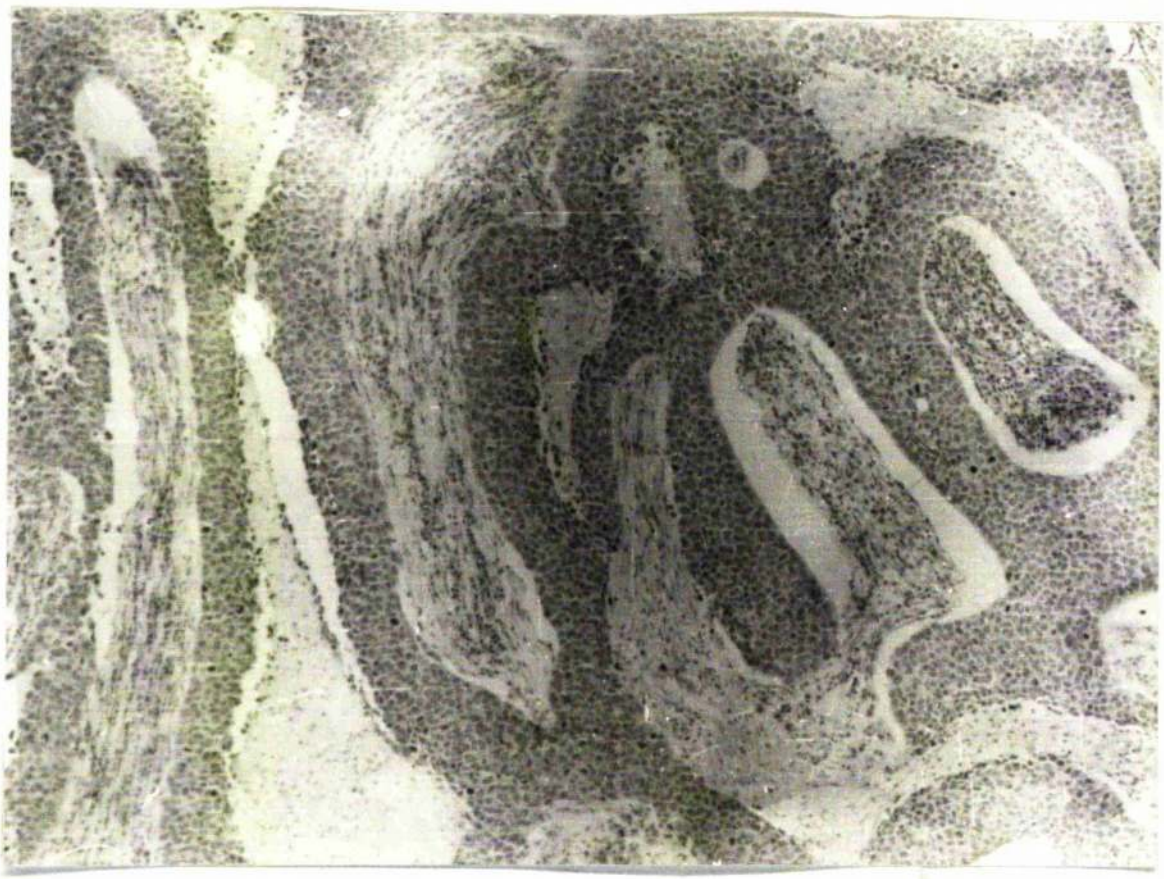


FIGURE 65: Medullary carcinoma with polymorph infiltration. Observe mosaic pattern, central fibrous tissue scanty and surrounded by malignant sheet of cells.

Haematoxylin and eosin X 100.

PLATE 66.

Medullary Carcinoma

FIGURE 66: Medullary carcinoma with polymorph infiltration, another pattern.

Haematoxylin and eosin X 100.

PLATE 67.

Medullary Carcinoma

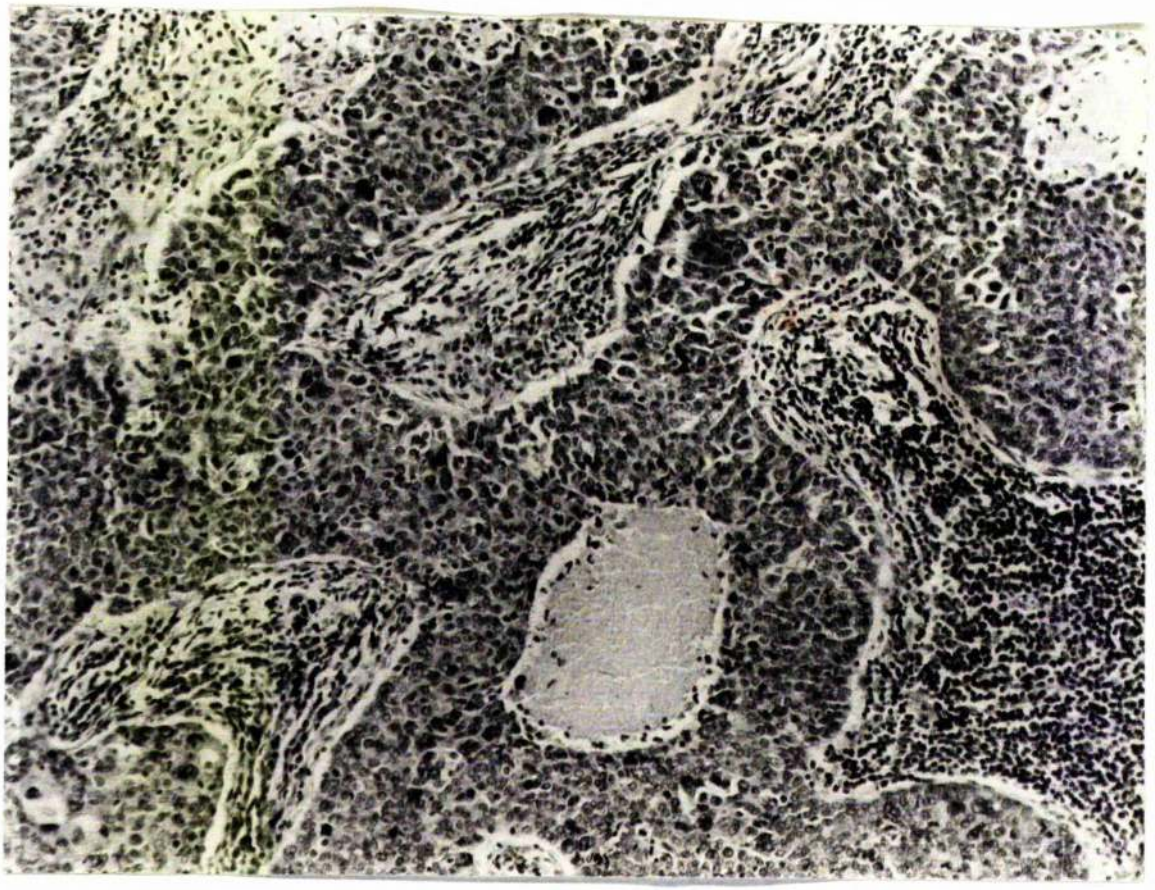


FIGURE 67: Medullary carcinoma with mixed lymph/ plasma cell and polymorph infiltration.

Haematoxylin and eosin X 200.

PLATE 68.

Medullary Carcinoma

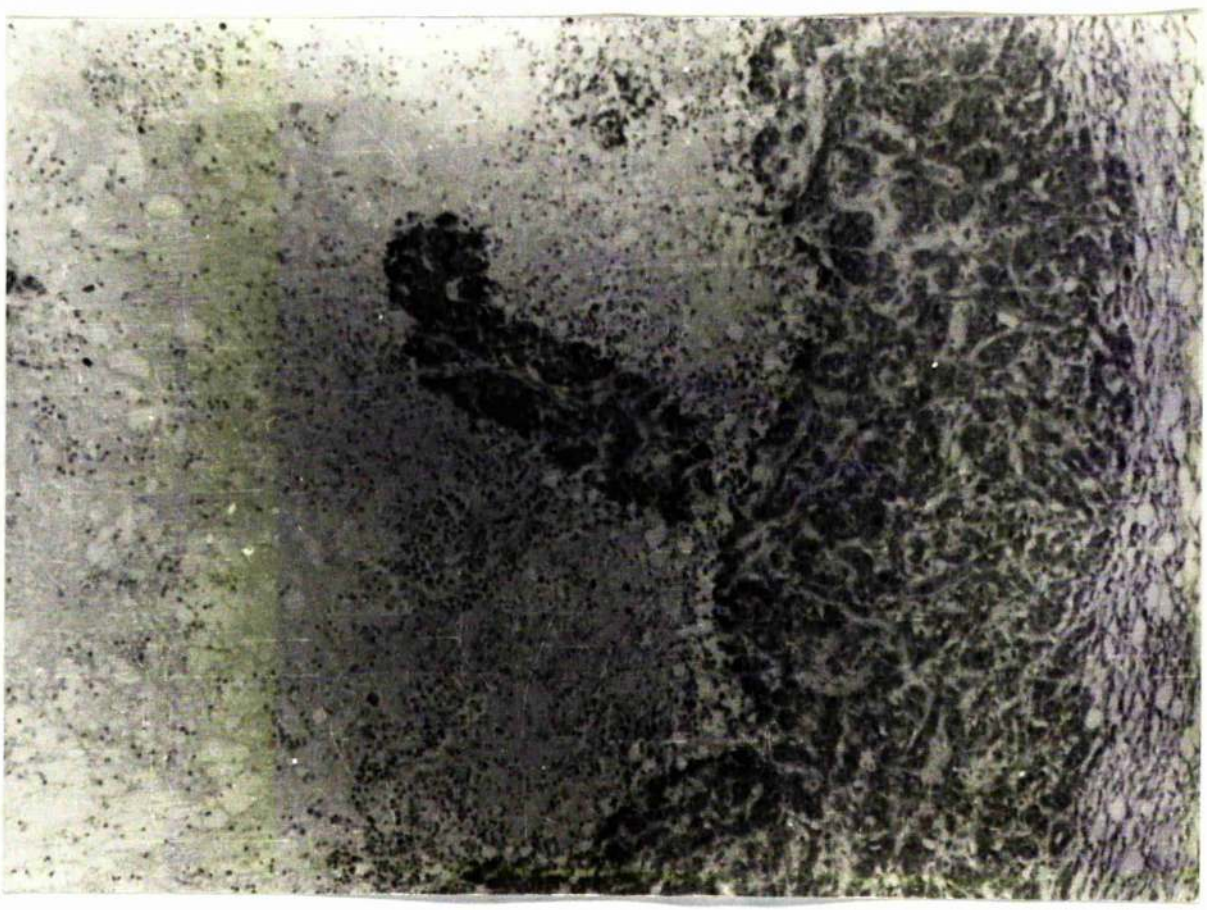


FIGURE 68: Medullary carcinoma with neither lympho/ plasma cell nor polymorph infiltration. Observe the ominious absence of host cellular reaction and area of necrosis

Haematoxylin and eosin X 100.

PLATE 69.

Medullary Carcinoma

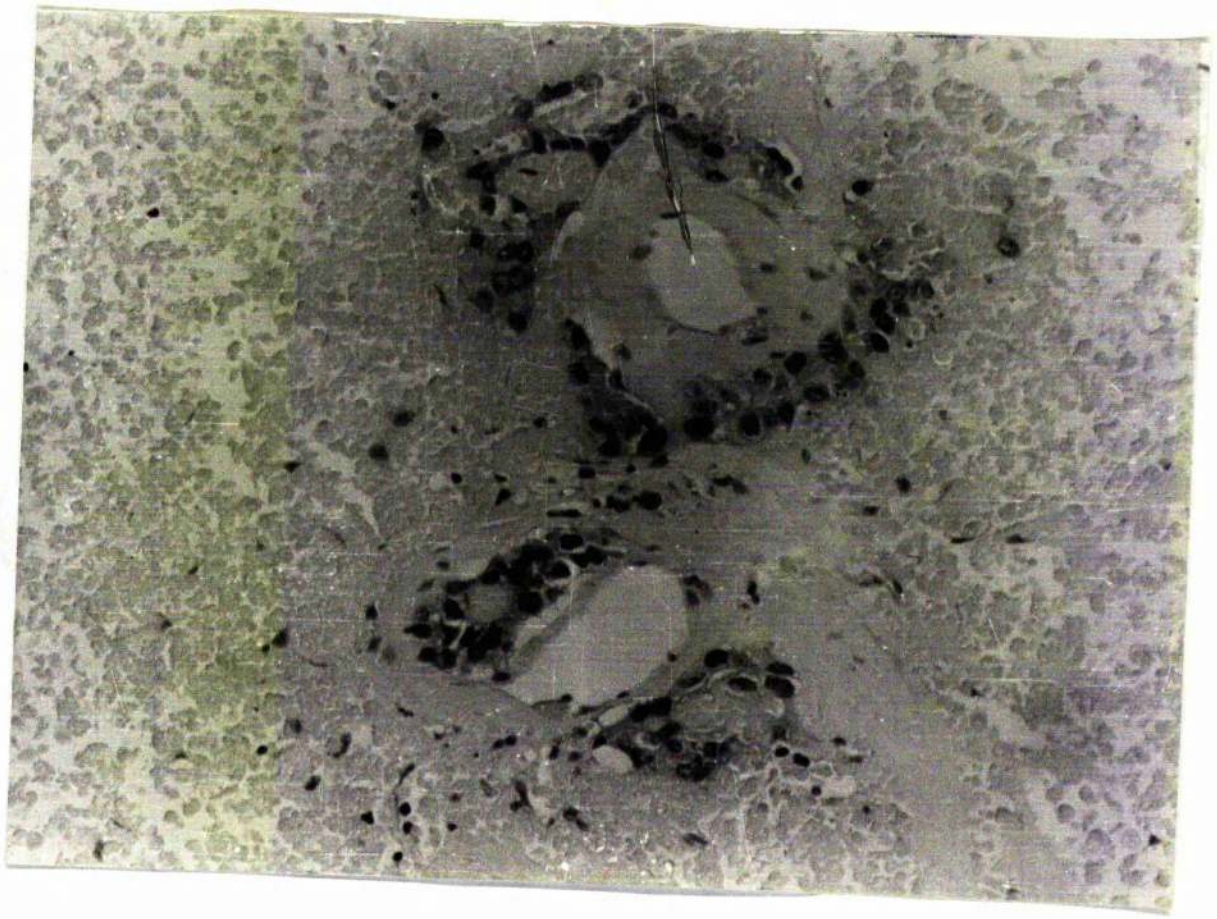


FIGURE 69: Observe massive coagulative necrosis in medullary carcinoma with no host cellular reaction.

Haematoxylin and eosin X 200.

PLATE 70.

Circumscribed Carcinoma

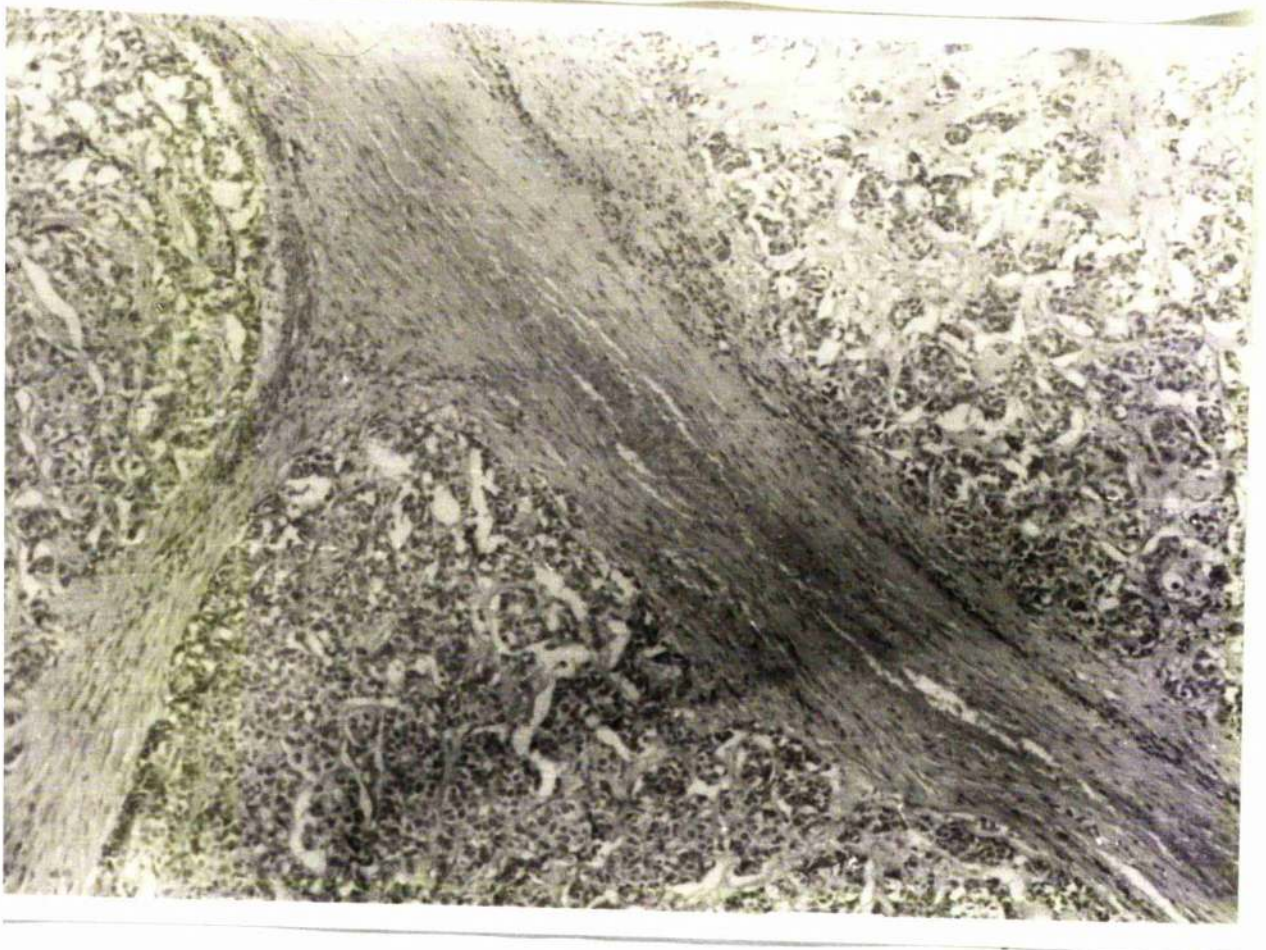


FIGURE 70: Multilobulated circumscribed carcinoma with fibrous septa separating malignant lobules.

Haematoxylin and eosin X 200.

PLATE 71.

Circumscribed Carcinoma

FIGURE 71: Multilobulated circumscribed carcinoma. Observe peripheral borders of maligaant lobules heavily infiltrated by lympho/plasma cells.

Haematoxylin and eosin X 100.

PLATE 72.

Circumscribed Carcinoma

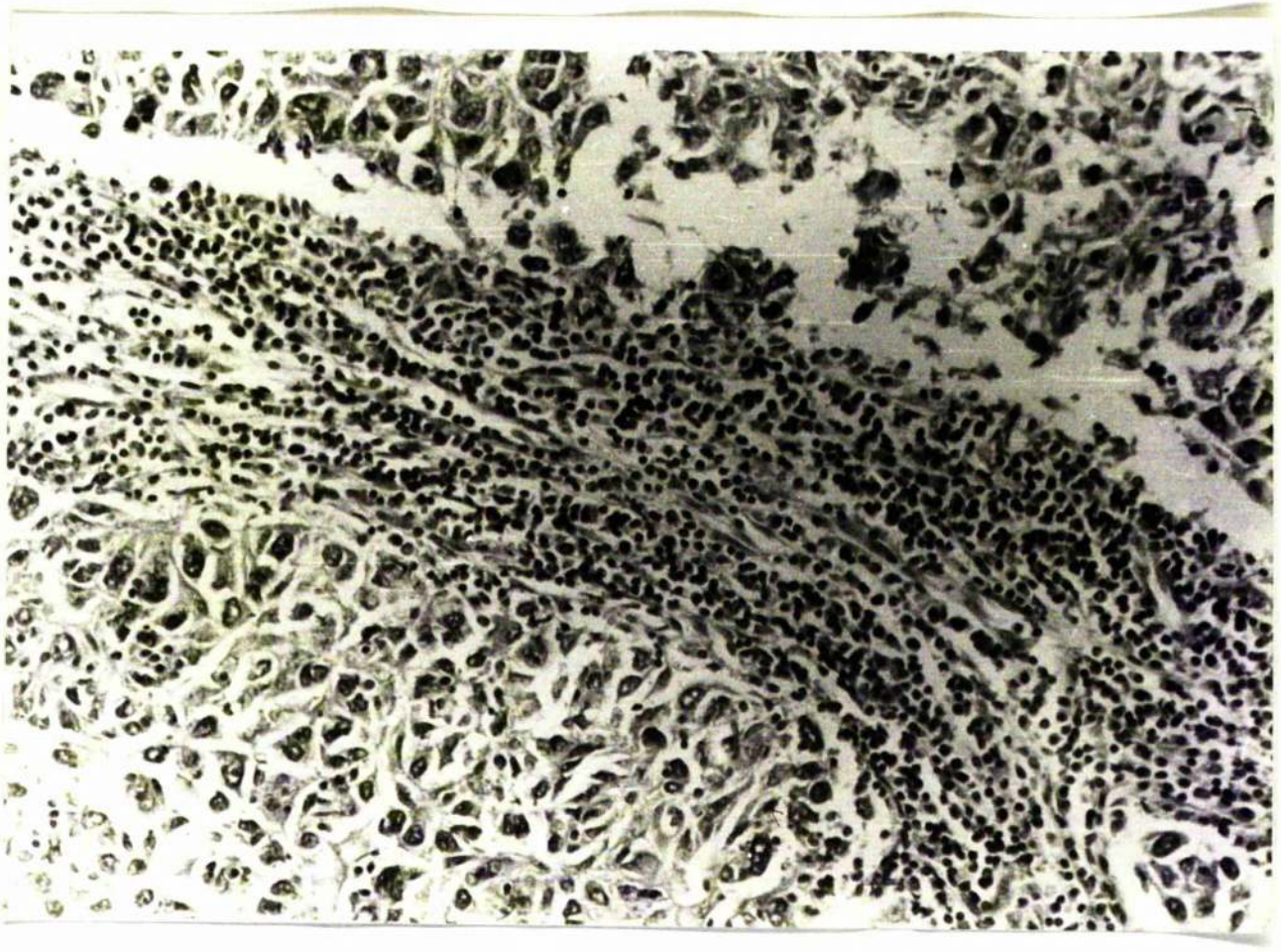


FIGURE 72: High-power view of fig. 71 showing details of peripherally located lympho/plasma cells.

Haematoxylin and eosin X 200.

PLATE 73.

Circumscribed Carcinoma

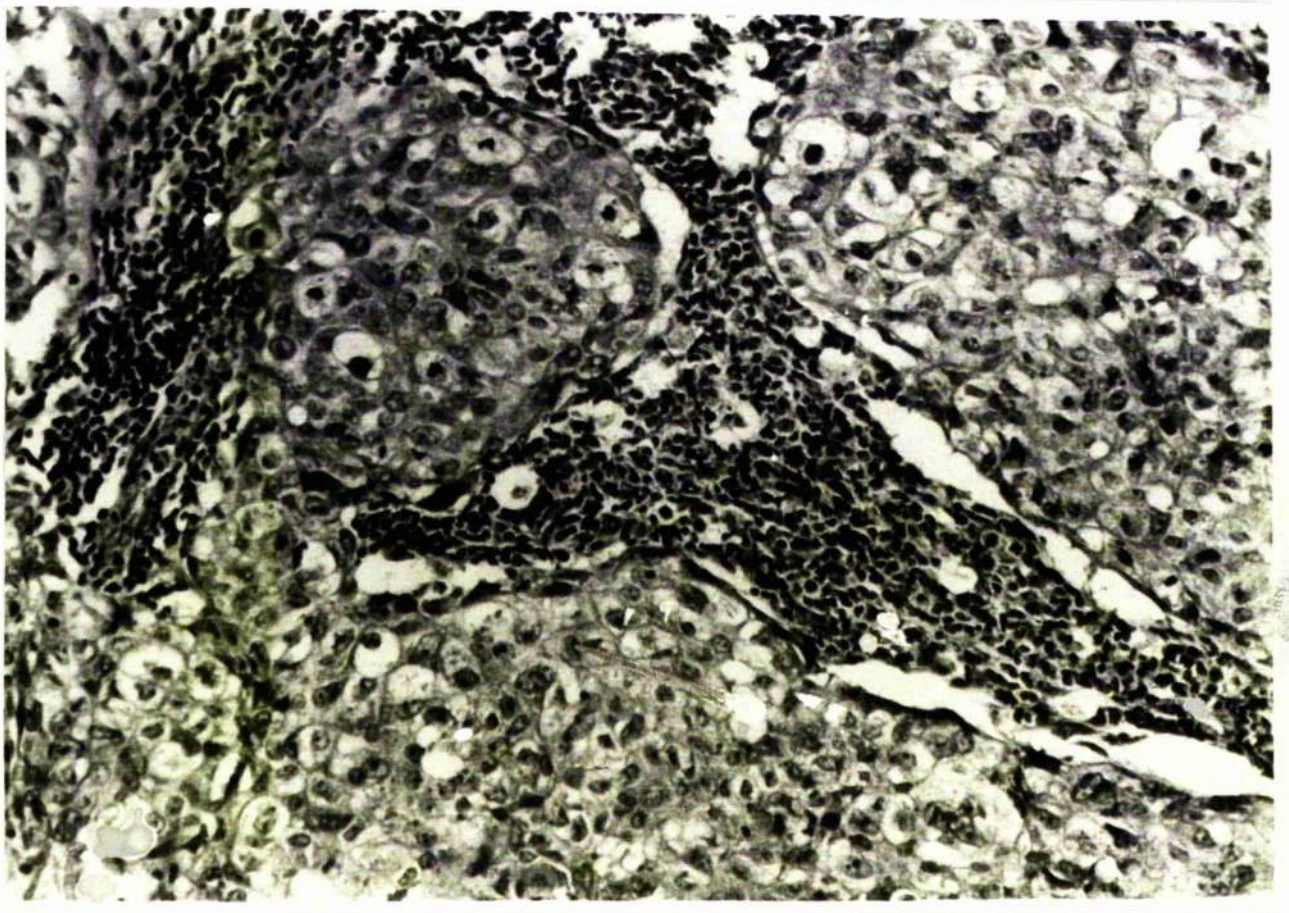


FIGURE 73: Medullary carcinoma with lympho/plasma cells. Contrast with figs. 70, 71 and 72.

Haematoxylin and eosin X 290.

PLATE 74.

Circumscribed Carcinoma

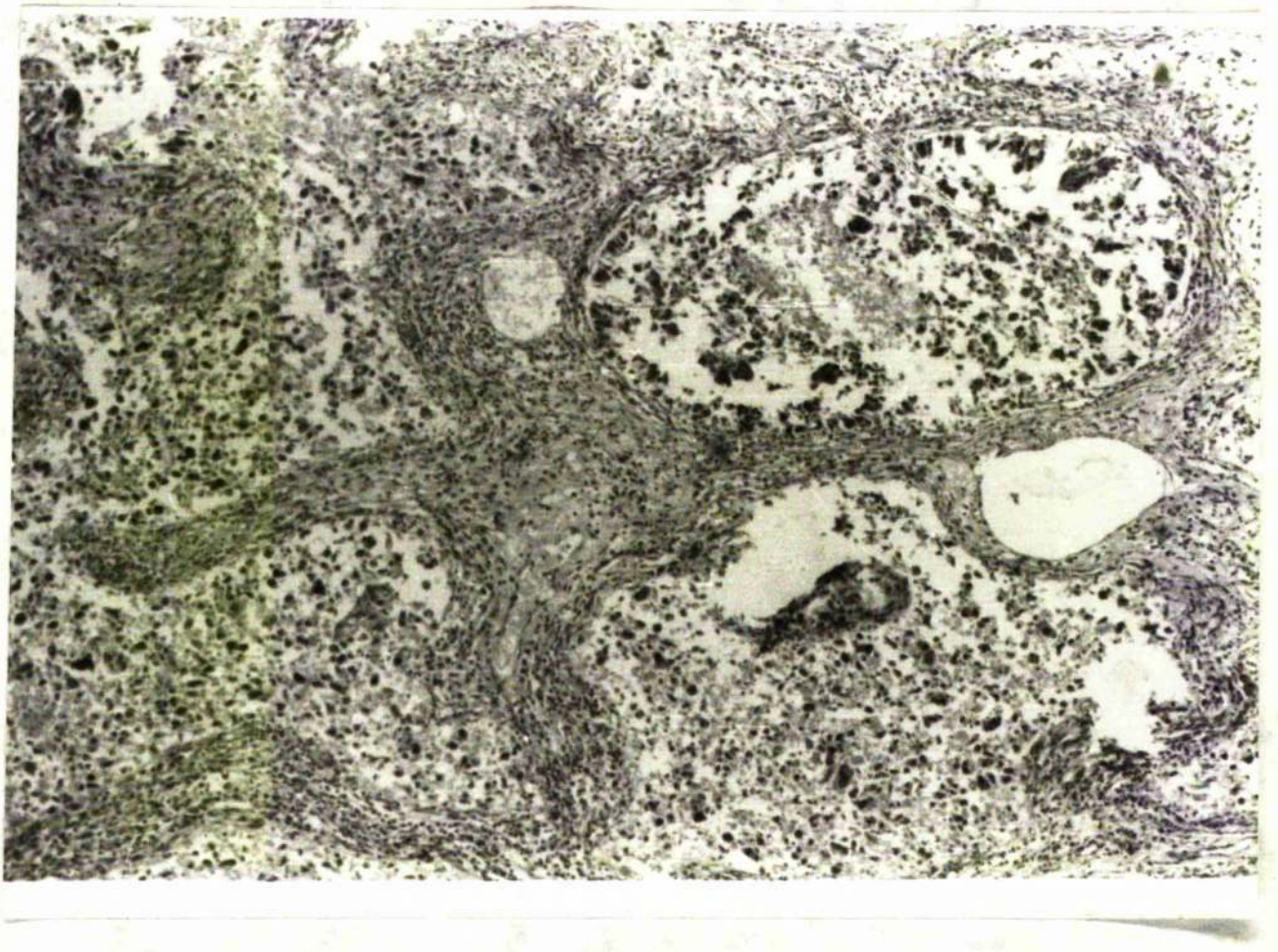


FIGURE 74: Multilobulated circumscribed carcinoma. Observe fibrous septa distinctly surrounding each malignant lobule.

Haematoxylin and eosin X 3200;

PLATE 75.

Circumscribed Carcinoma

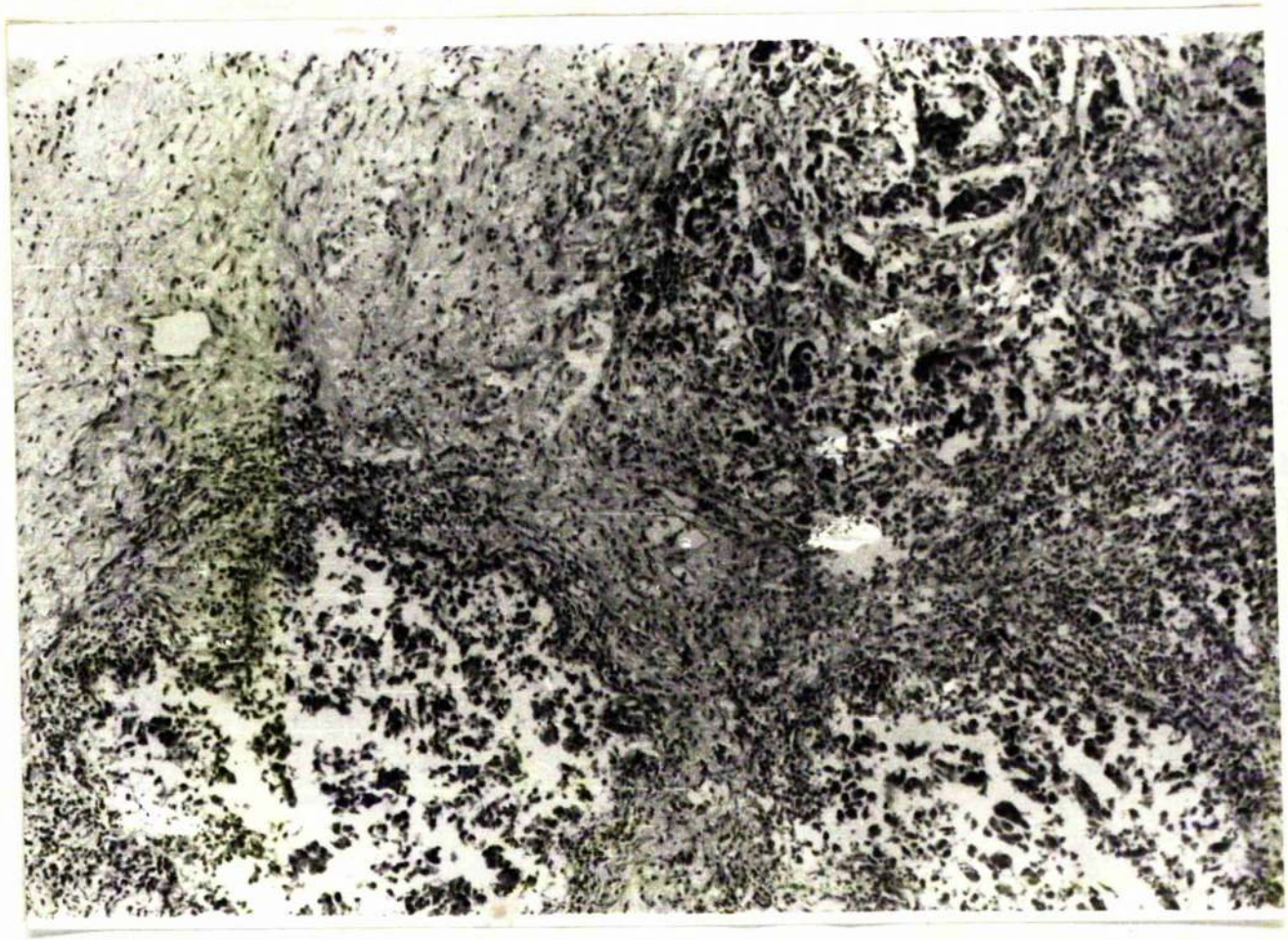


FIGURE 75: Circumscribed carcinoma. Observe fibrous septa originating from the main tumour capsule and ramifying centrally.

Haematoxylin and eosin X 100.

PLATE 76.

Circumscribed Carcinoma

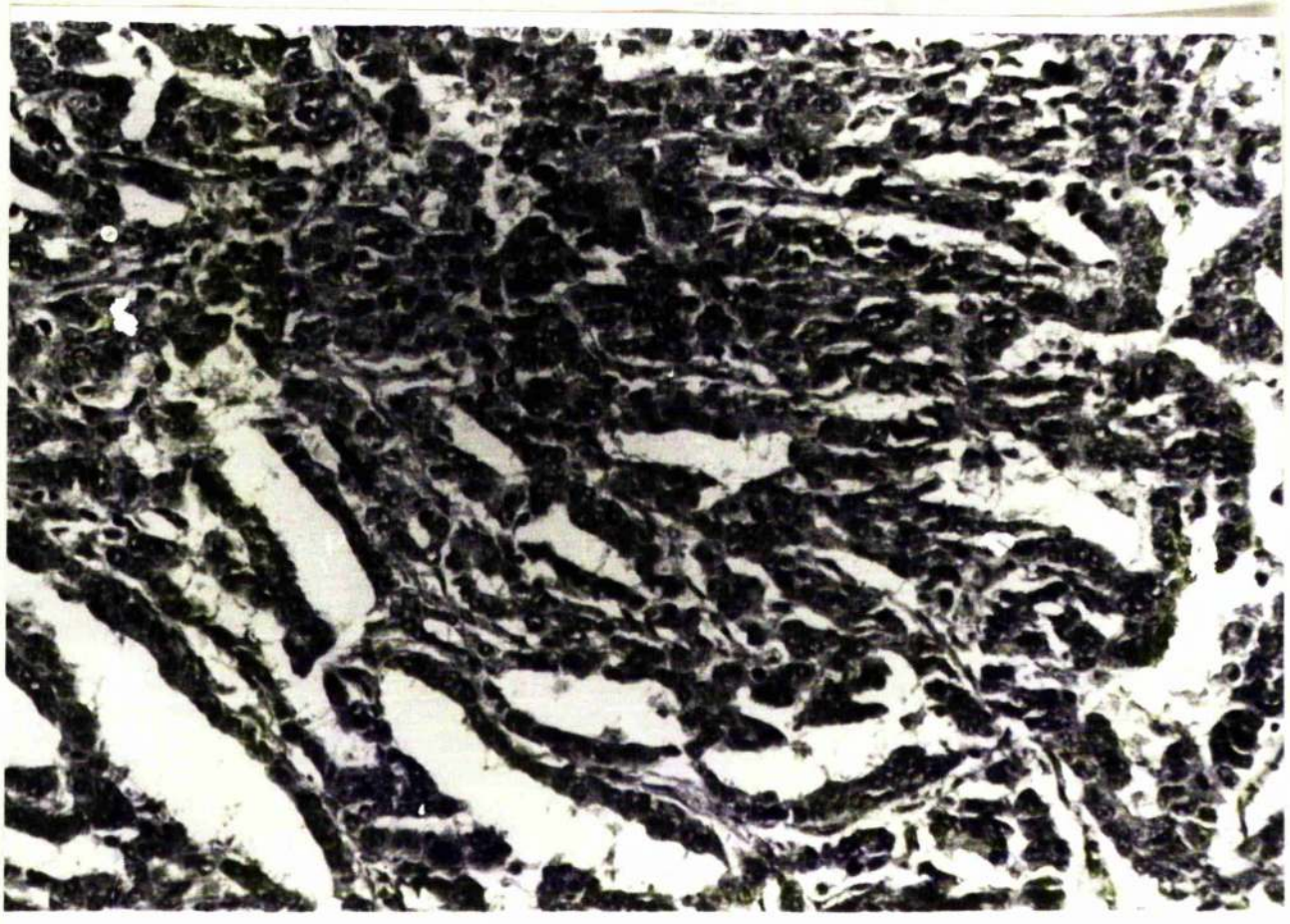


FIGURE 76: Circumscribed carcinoma with papillary structure.

Haematoxylin and eosin X 290.

PLATE 77.

Circumscribed Carcinoma

FIGURE 77: Circumscribed carcinoma with tubular and glandular structures in a malignant lobule.

Haematoxylin and eosin X 260.

PLATE 78.

Papillary Carcinoma (Male 55)

FIGURE 78: Intracystic papillary carcinoma. Observe the dilated cysts lined by malignant epithelial cells which are single or multilayered.

Haematoxylin and eosin X 100.

PLATE 79.

Papillary Carcinoma (Male 55)

FIGURE 79: High-power view of an area of fig. 78 showing heaped up malignant cells with others in single layer.

Haematoxylin and eosin X 290.

PLATE 80.

Papillary Carcinoma (Male 55)

FIGURE 80: Papillary carcinoma. Observe early formation of malignant syncytial coreless paipillae projecting into the centre of cystic cavity.

Haematoxylin and eosin X 440.

PLATE 81.

Papillary Carcinoma (Male 55)

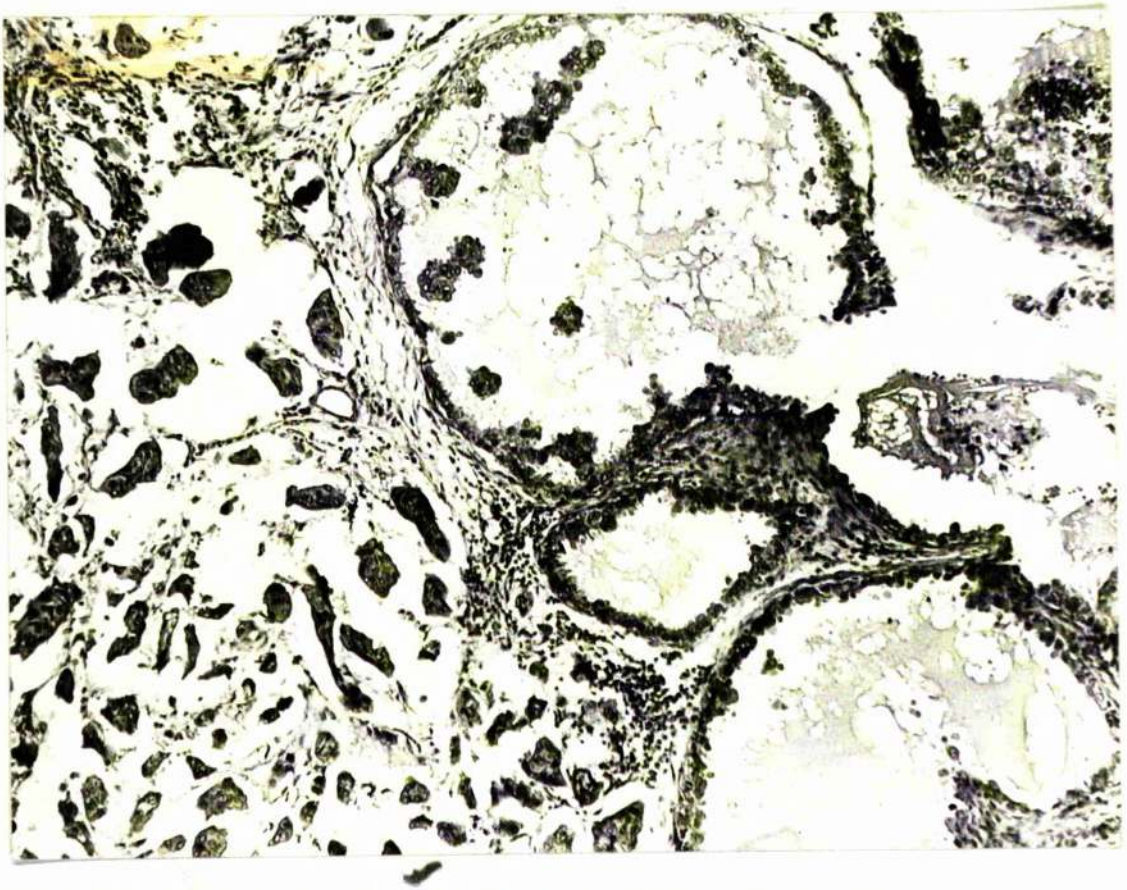


FIGURE 81: Intracystic papillary carcinoma with invasive coreless papillary carcinoma. Observe the nests of malignant cells in clear spaces.

Haematoxylin and eosin X 92.

PLATE 82.

Papillary Carcinoma (Male 55)

FIGURE 82: Invasive papillary carcinoma showing early cart-wheel pattern formation.

Haematoxylin and eosin X 200.

PLATE 83.

Papillary Carcinoma (Male 55)

FIGURE 83: Invasive papillary carcinoma metastatic to a lymph node. Observe the nest of malignant coreless papillae in clear spaces.

Haematoxylin and eosin X 100.

PLATE 84.

Papillary Carcinoma (Male Adult)

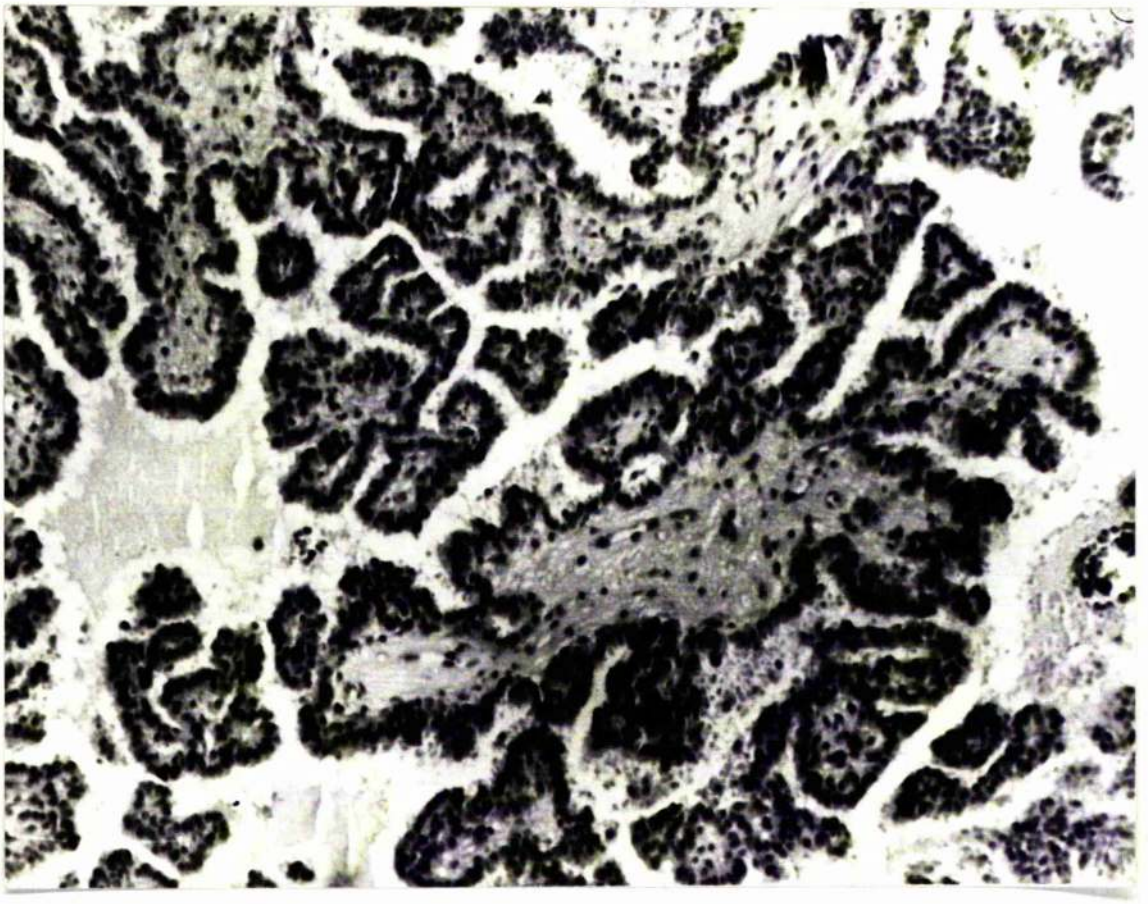


FIGURE 84: **Invasive papillary carcinoma. Observe the malignant papillae with central fibro-vascular connective tissue cores.**

Haematoxylin and eosin X 100.

PLATE 85.

Papillary Carcinoma (Male Adult)

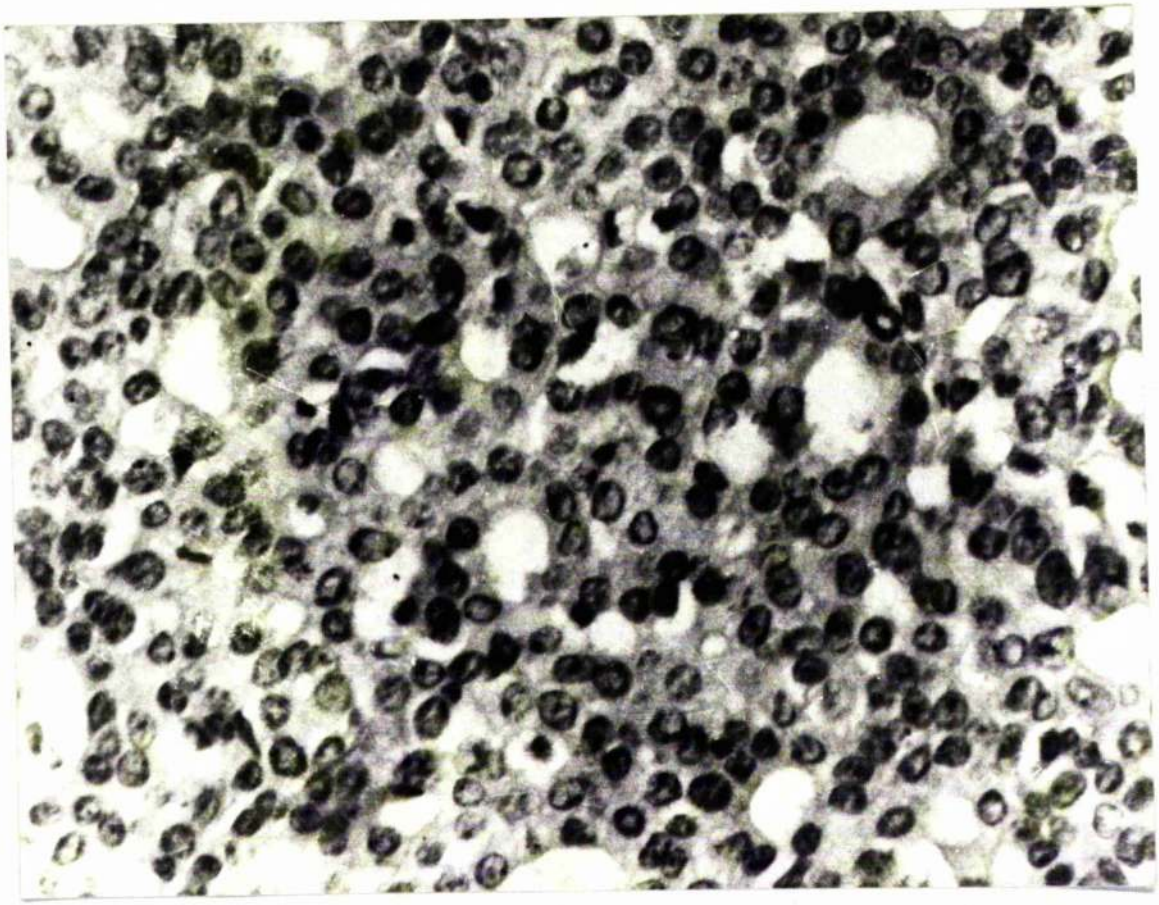


FIGURE 85: Invasive papillary carcinoma with cribirform pattern.

Haematoxylin and eosin X 290.

PLATE 86.

Papillary Carcinoma (Male Adult)

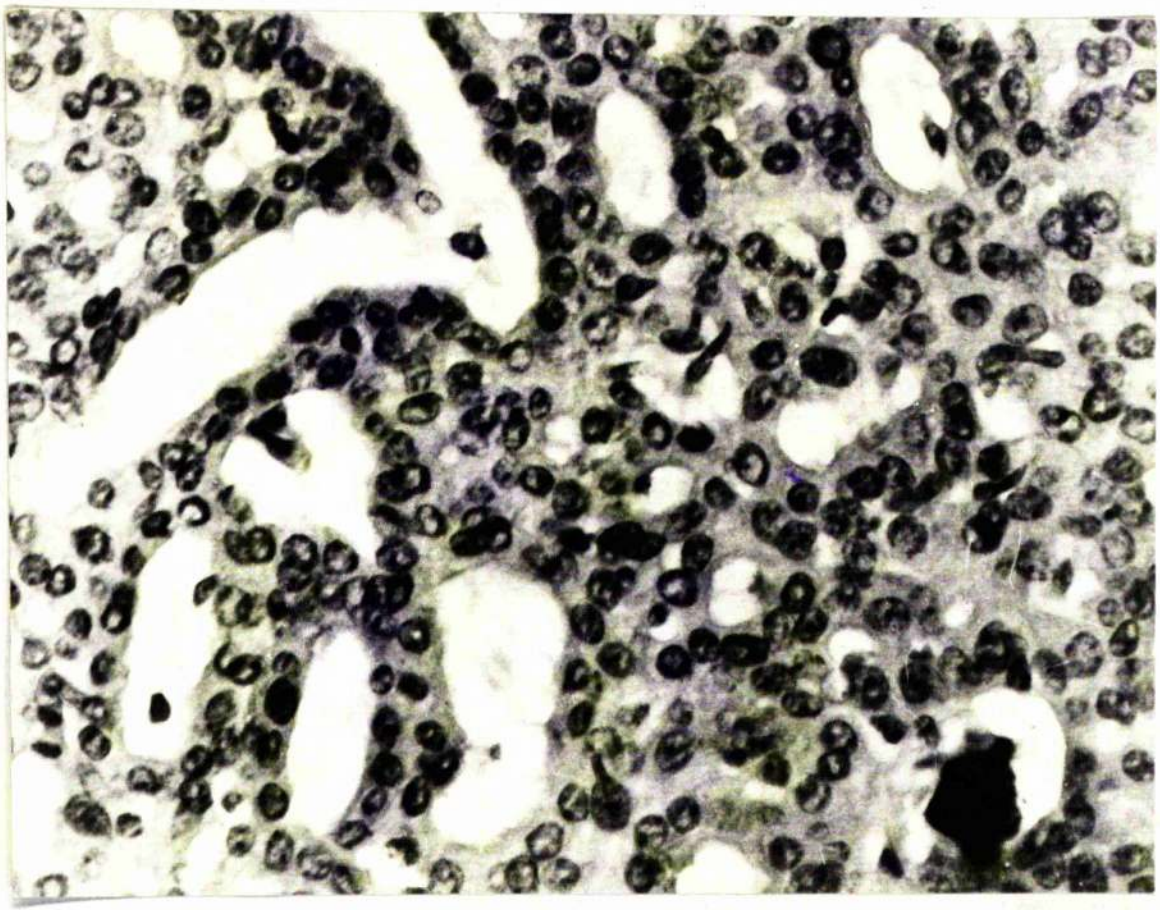


FIGURE 86: High-power view of fig. 85. Observe the microcalculus (Extreme concer left).

Haematoxylin and eosin X 290.

PLATE 87.

Papillary Carcinoma (Male Adult)

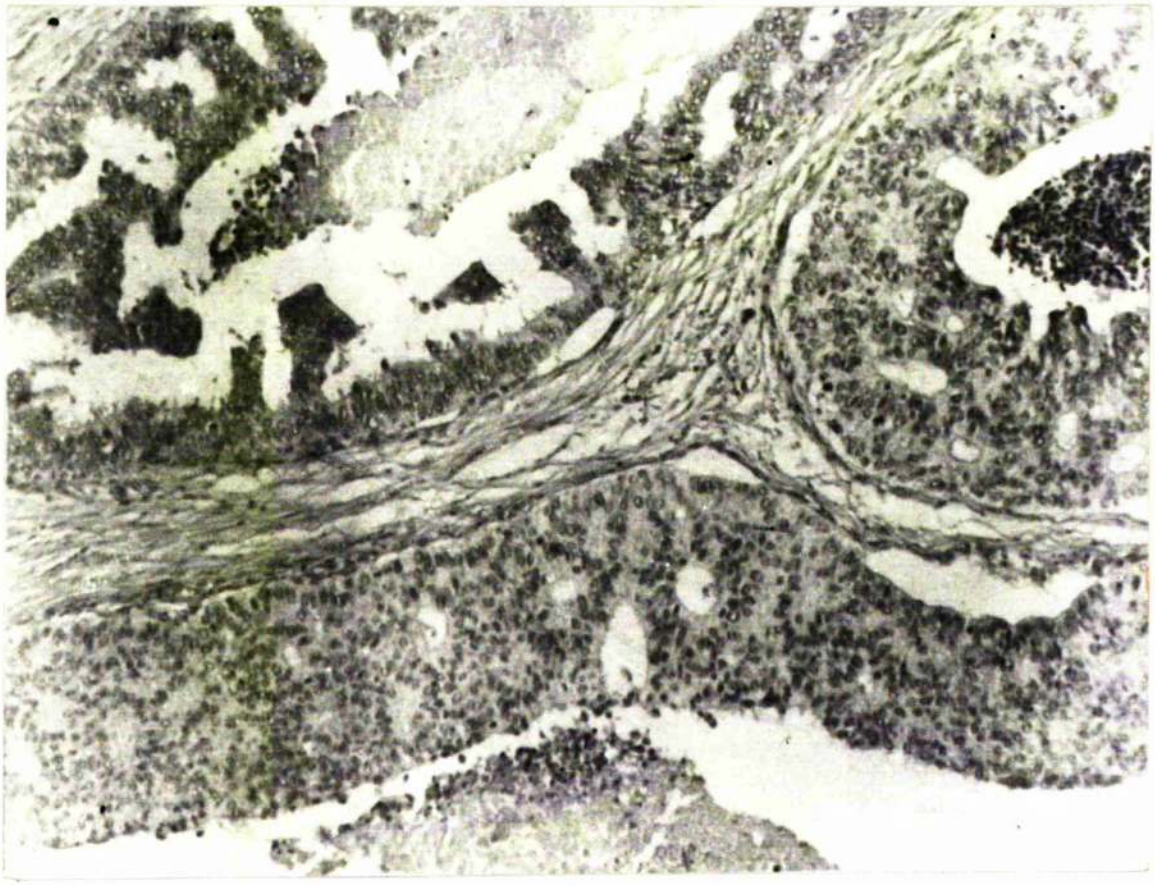


FIGURE 87: Invasive papillary carcinoma showing malignant intracystic coreless papillae (upper concer) and cribriform pattern in combination (below and to the right).

Haematoxylin and eosin X 100.

PLATE 88.

On **Papillary Carcinoma (Male adult)**

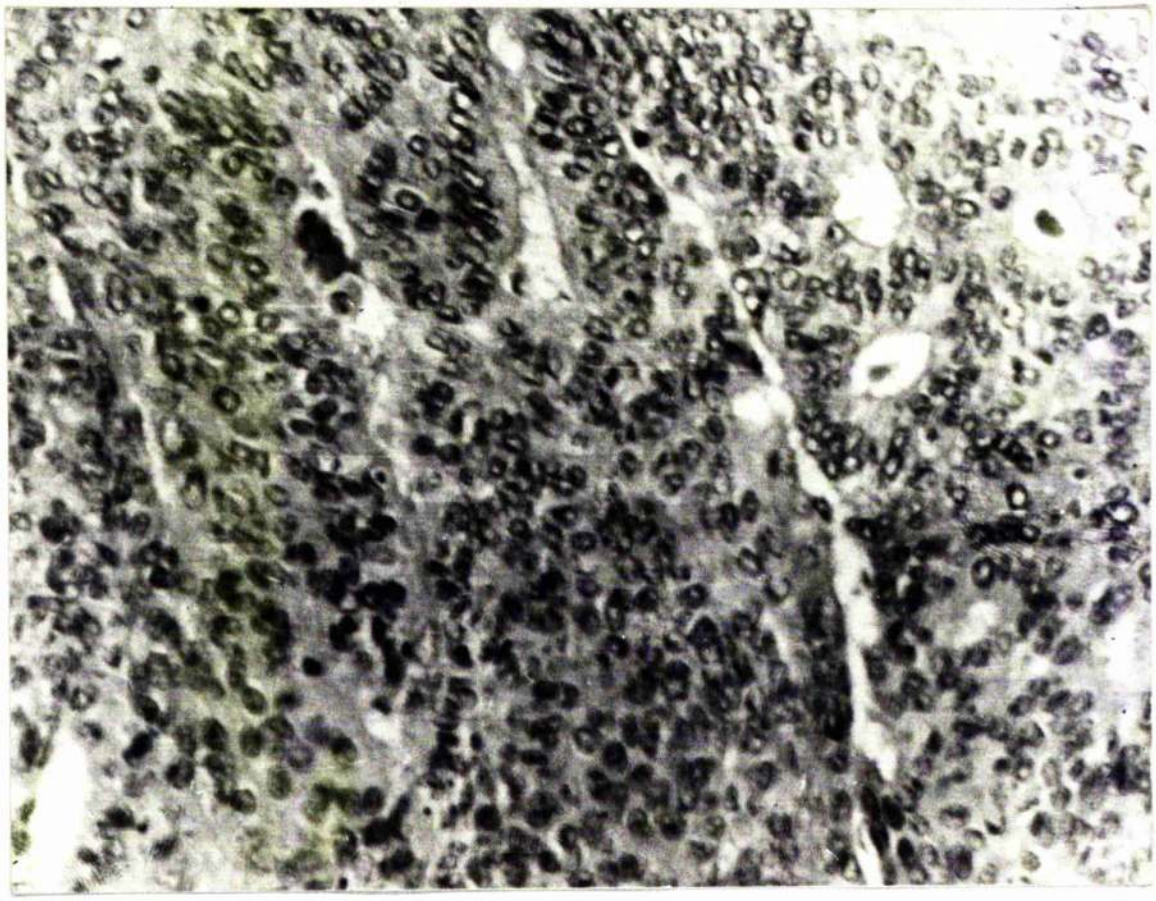


FIGURE 88: **Invasive papillary carcinoma with solid** (left) **and cribriform** (right) patterns.

Haematoxylin and eosin X 196.

PLATE 89.

Invasive Papillary Carcinoma (Male 55)

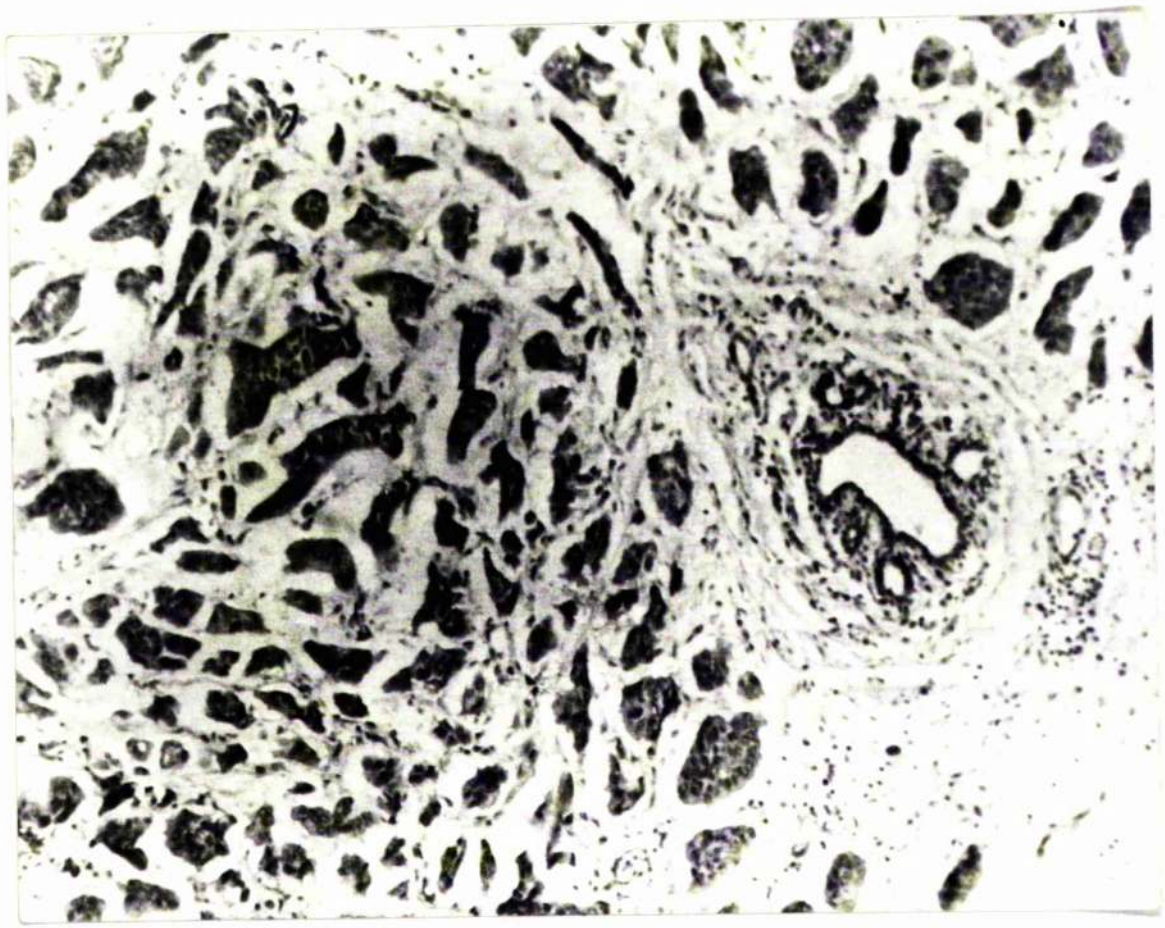


FIGURE 89: Invasive papillary carcinoma in a male patient. Observe combination of short and and elongated coreless malignant papillae around a cystically dilated duct.

Haematoxylin and eosin X 100.

PLATE 90.

Invasive Papillary Carcinoma (Male 55)

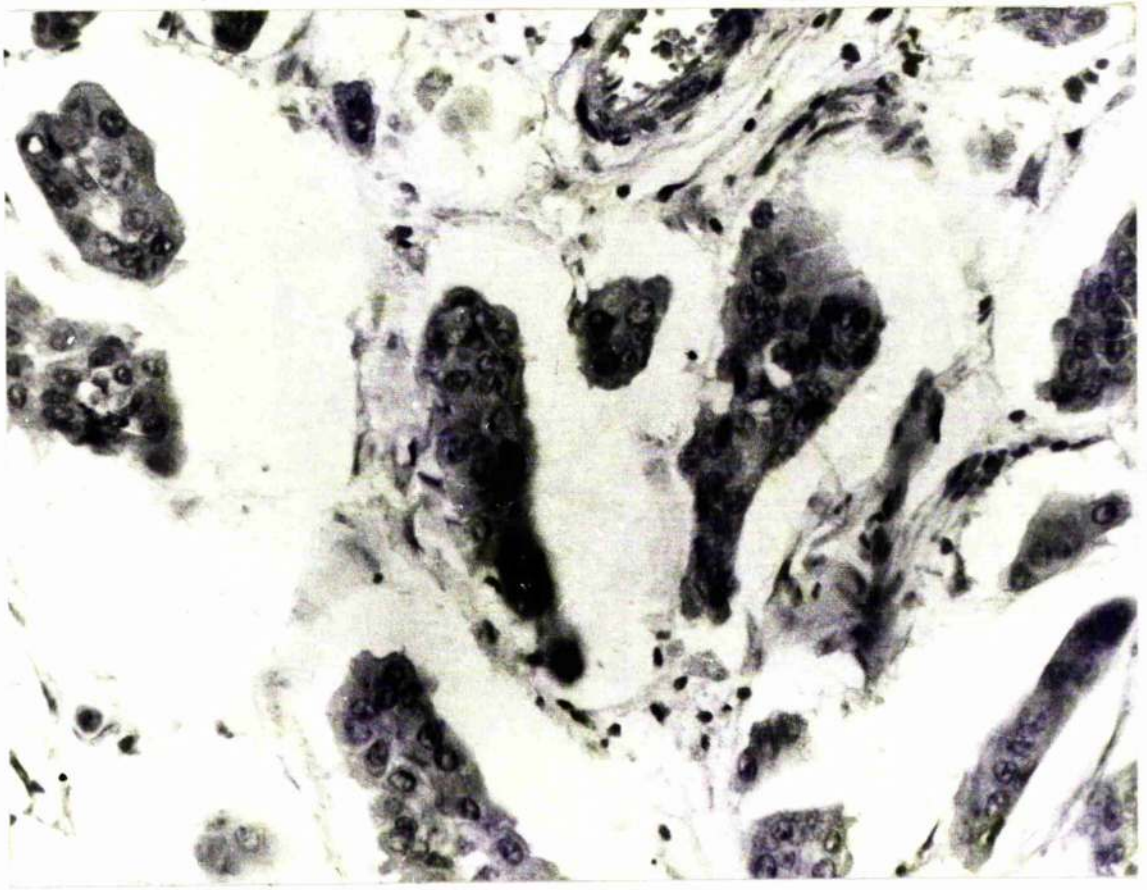


FIGURE 90: High-power view of fig. 89 showing clear spaces surrounding the malignant papillae. Note the scanty stroma.

Haematoxylin and eosin X 200.

PLATE 91.

Invasive Papillary Carcinoma (Male 55)

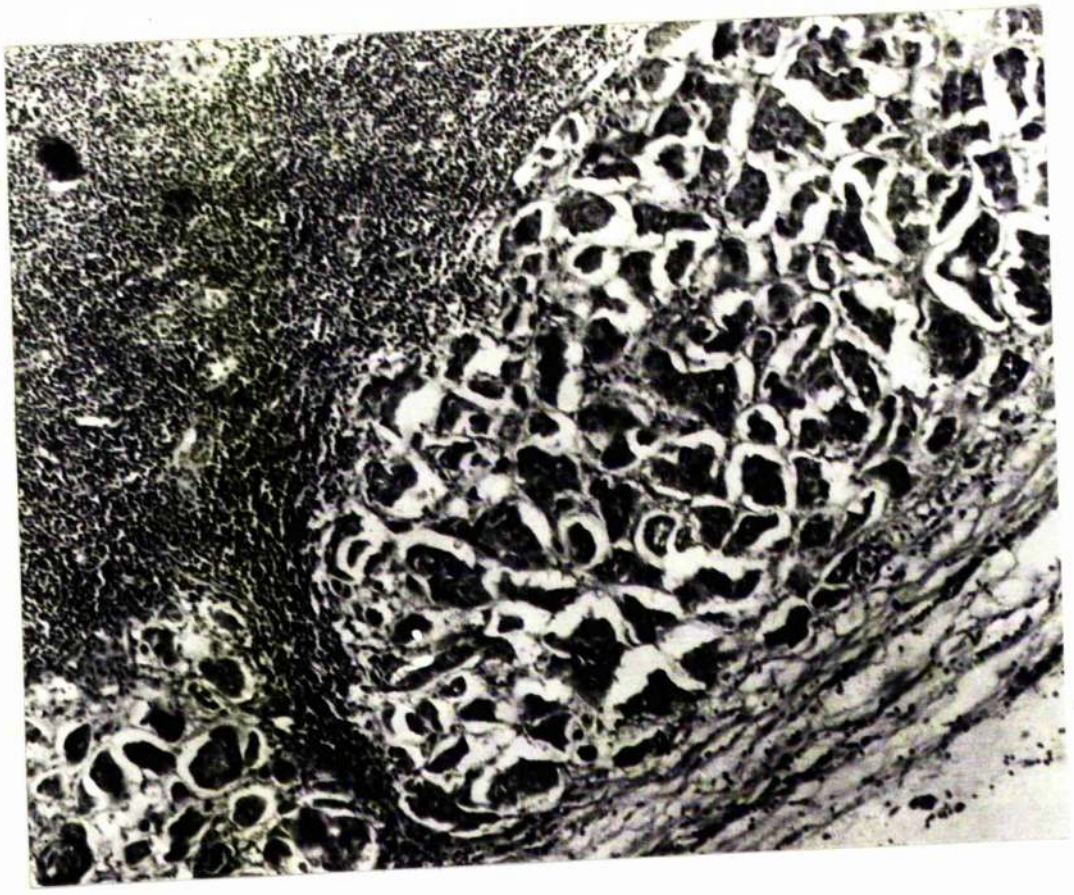


FIGURE 91: Invasive papillary carcinoma metastatic to a lymph node.

Haematoxylin and eosin X 92.

PLATE 92.

Paget's Disease of the Nipple

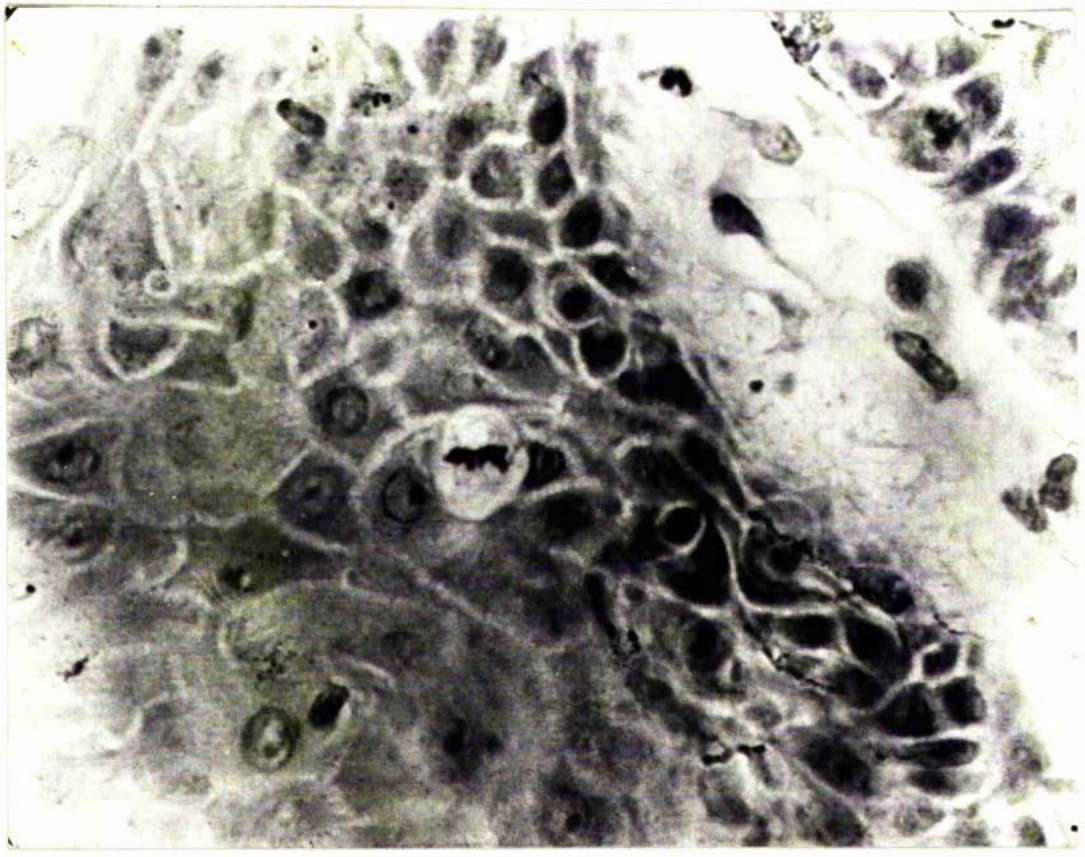


FIGURE 92: Paget cell in mitosis seen in invaded nipple epidermis.

Haematoxylin and eosin X 700.

PLATE 93.

Paget's Disease of the Nipple

FIGURE 93: Paget cells may be seen in epidermis of rete pegs or in hair follicles.

Haematoxylin and eosin X 100.

PLATE 94.

Paget's Disease of the Nipple

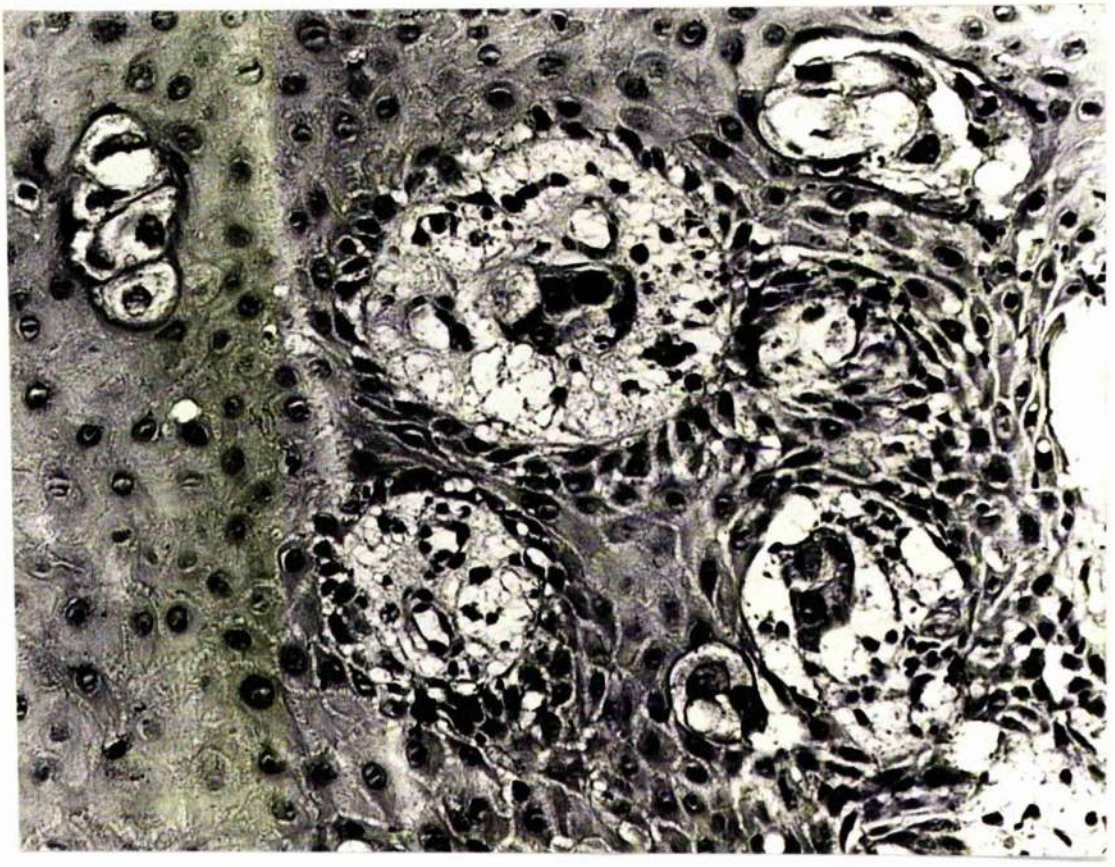


FIGURE 94: Clumps or nests of Paget cells in nipple epidermis.

Haematoxylin and eosin X 175.

PLATE 95.

Paget's Disease of the Nipple

FIGURE 95: Patet's cells compressing epidermal squamous cells into elongated shapes to form net-work.

Haematoxylin and eosin X 175.

PLATE 96.

Paget's Disease of the Nipple

FIGURE 96: **High-power view of fig. 95 showing Paget's cells with engulfed melanin granules mimicking intraepidermal malignant melanoma.**

Haematoxylin and eosin X 700.

PLATE 97.

Paget's Disease of the Nipple

FIGURE 97: Paget's cells confined mainly to the nipple epidermis. Observe hos inflammatory cells in the upper dermis.

Haematoxylin and eosin X 96.

PLATE 98.

Paget's Disease of the Nipple

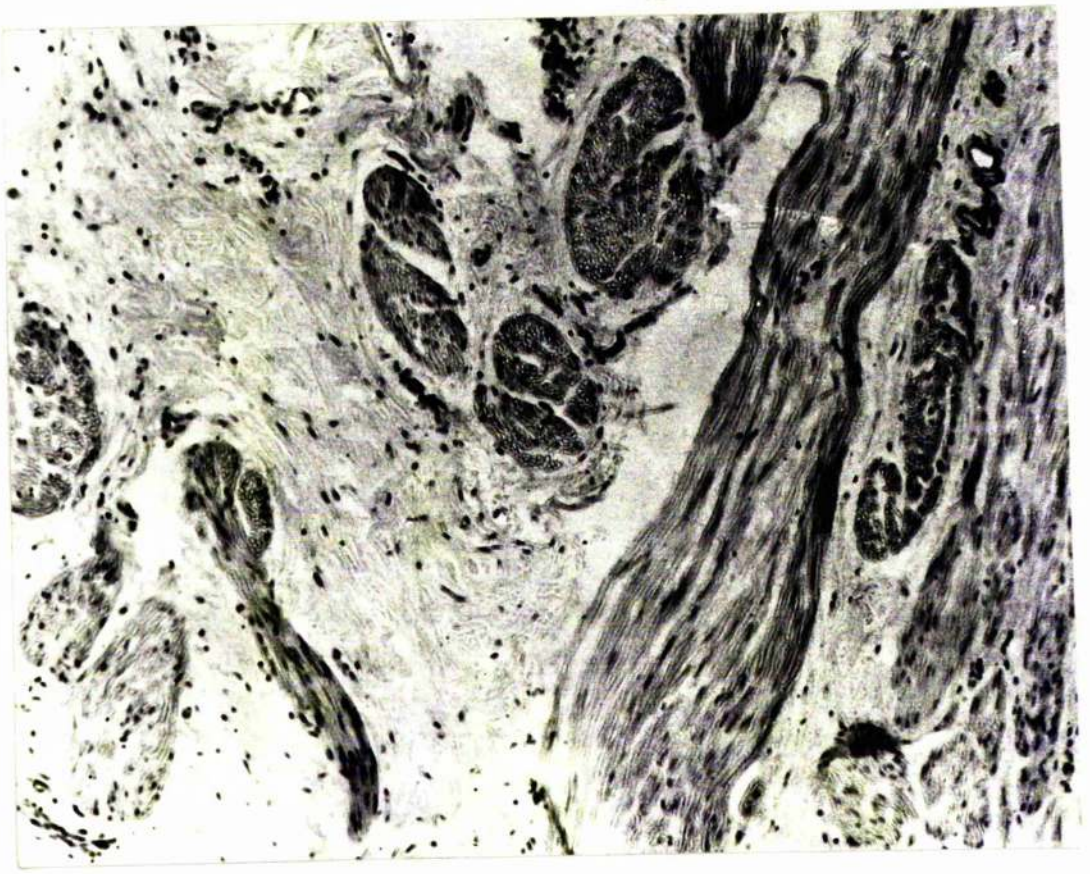


FIGURE 98: **Hypertrophied smooth muscle around a nipple that is invaded by Paget's cells,** may be responsible for erection of nipple in advanced Paget's disease.

PLATE 99.

Paget's Disease of the Nipple

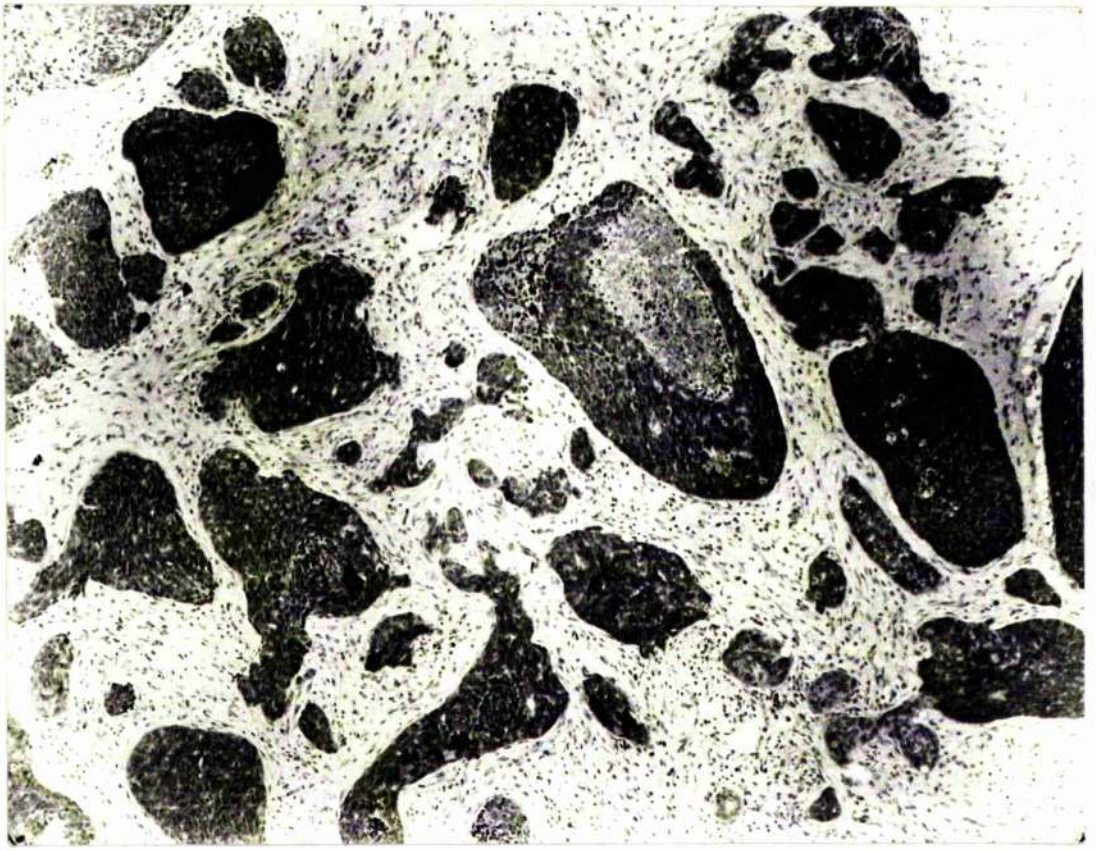


FIGURE 99: Intraductal carcinoma associated with Paget's cell in fig. 92.

Haematoxylin and eosin X 70.

PLATE 100.

Paget's Disease of the Nipple

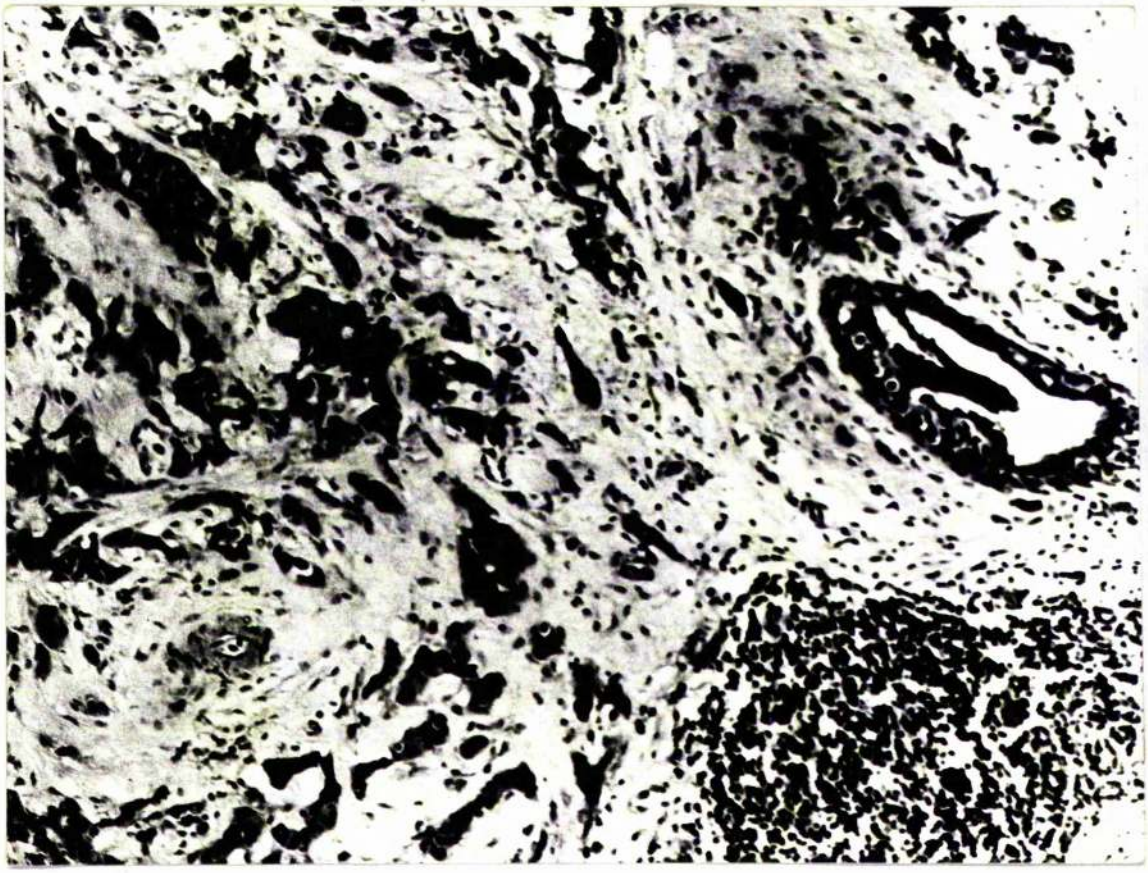


FIGURE 100: **Intraductal carcinoma with stromal invasion. Observe Paget's cells in an intraductal carcinoma (middle left).**

Haematoxylin and eosin X 96.

PLATE 101.

Paget's Disease of the Nipple

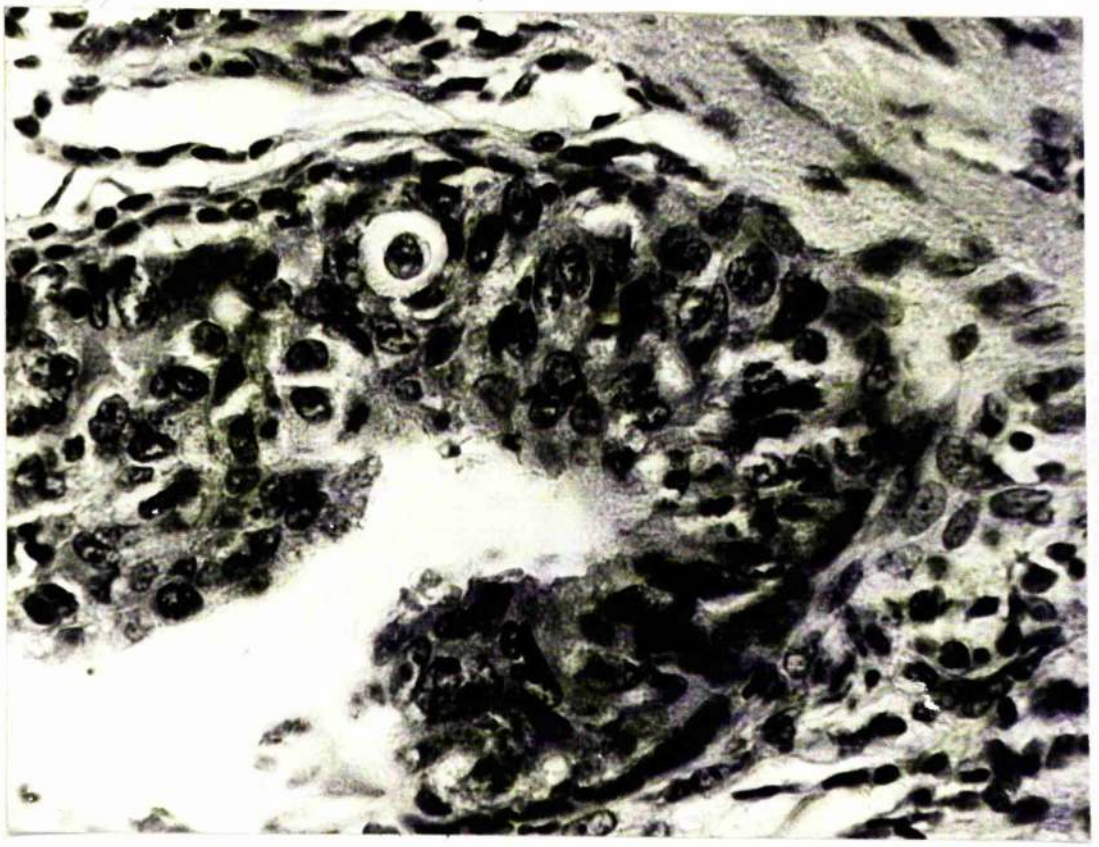


FIGURE 101: High-power view of fig. 100 showing Paget's cells.

Haematoxylin and eosin X 286.

PLATE 102.

Paget's Disease of the Nipple

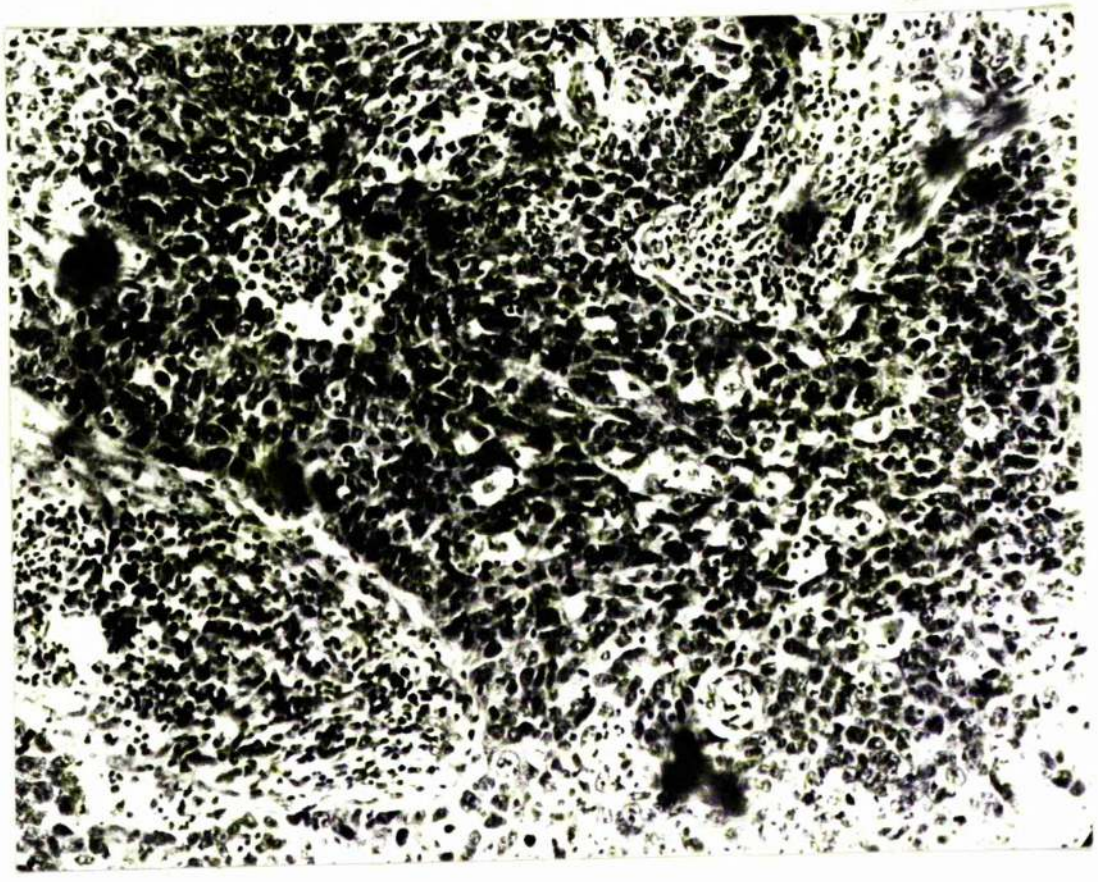


FIGURE 102: Typical syncytial medullary carcinoma with lympho/plasma cell infiltration associated with Paget's cells in fig. 93.

Haematoxylin and eosin X 175.

PLATE 103.

Paget's Disease of the Nipple

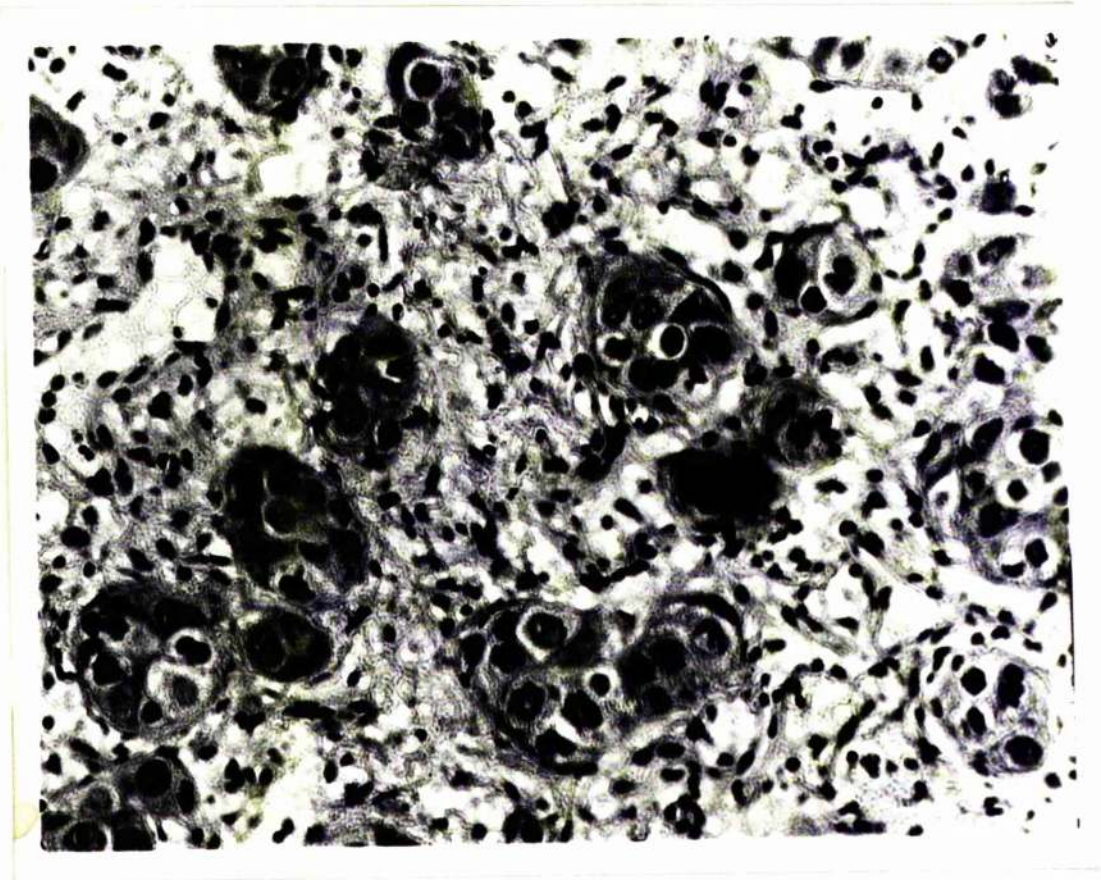


FIGURE 103: Invasive lobular carcinoma associated with nests of Paget's cells in fig. 94.

Haematoxylin and eosin X 195.

PLATE 104.

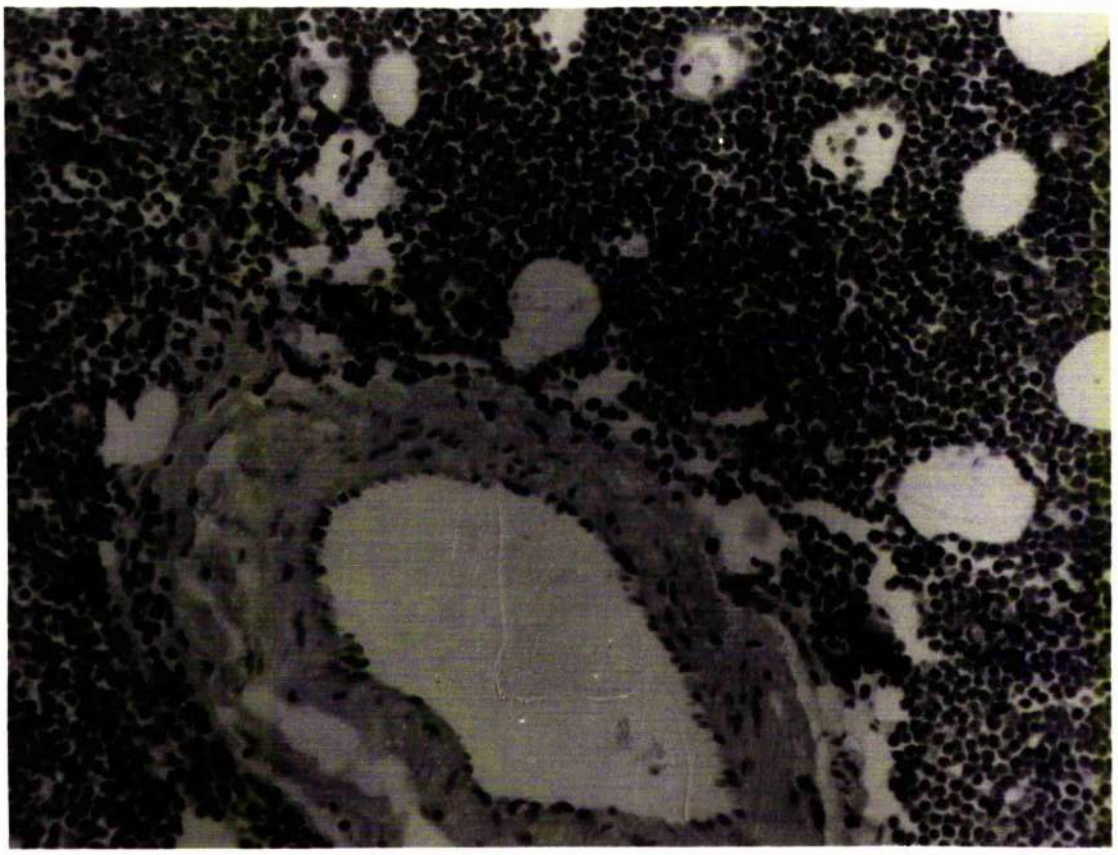


FIGURE 104: Primary Burkitt's lymphoma of breast. The starry sky pattern of Burkitt's lymphoma due to macrophages interspersed among undifferentiated lymphoid cells.

Haematoxylin and eosin X 100.

PLATE 105.

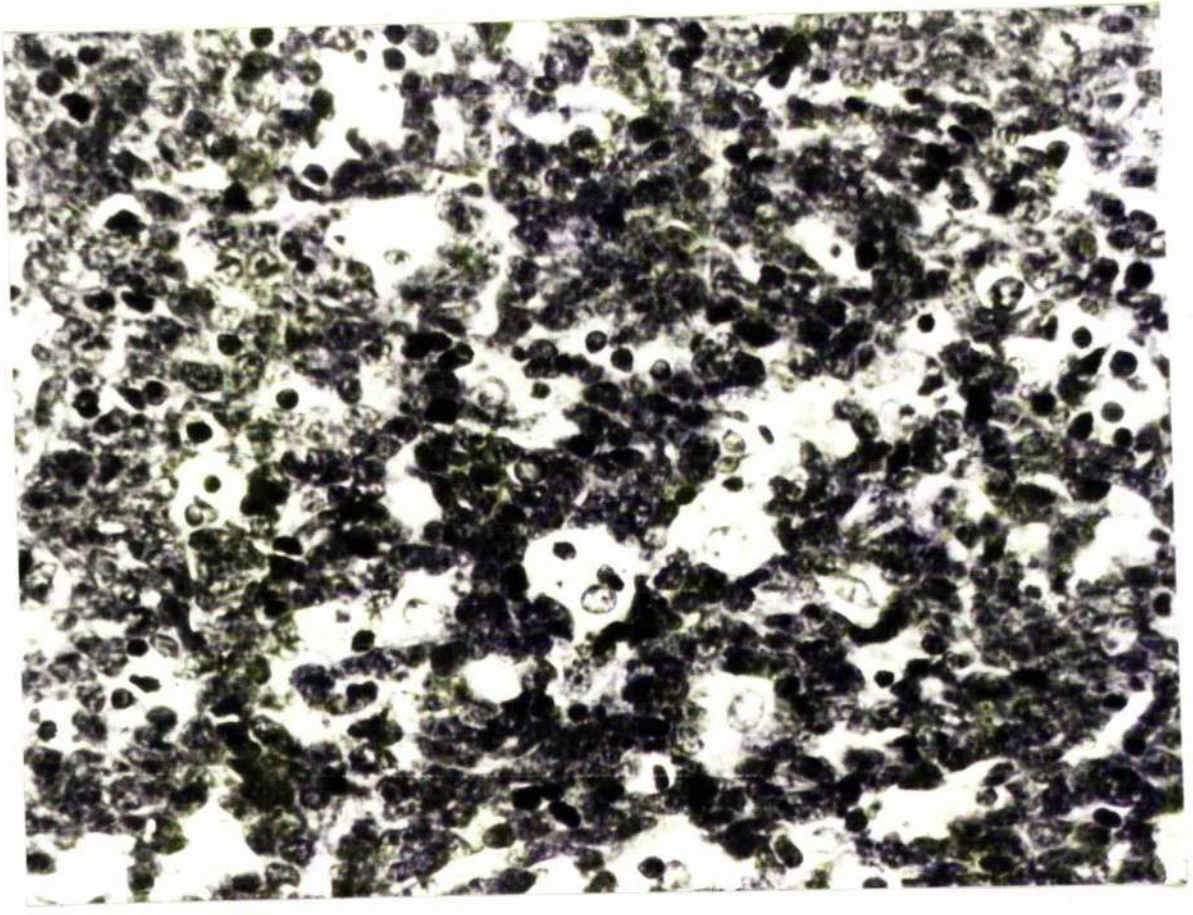


FIGURE 105: High-power view of fig. 104 showing macrophages with phagocytosed cellular and nuclear debris.

Haematoxylin and eosin X 440.

PLATE 106.

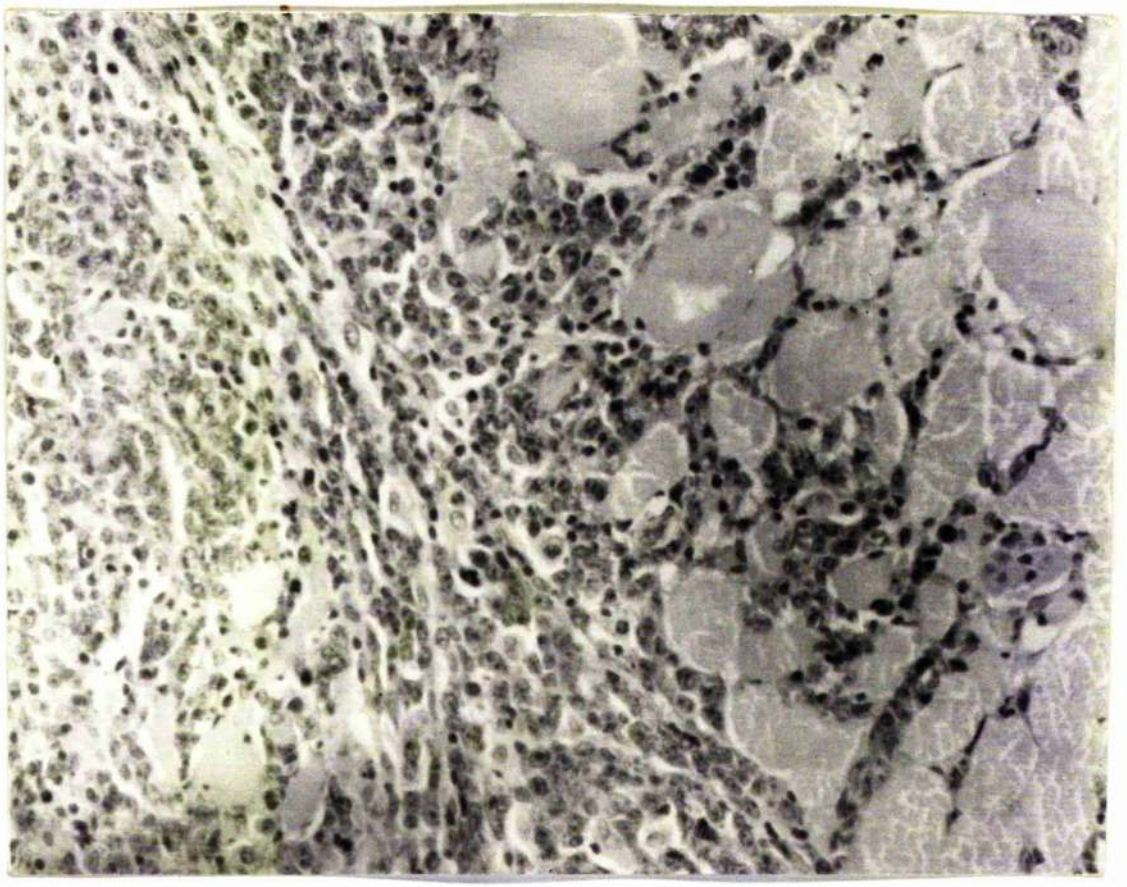


FIGURE 106: Primary Burkitt's lymphoma of breast. Observe muscular invasion by undifferentiated lymphoid cells.

Haematoxylin and eosin X 440.

PLATE 107.

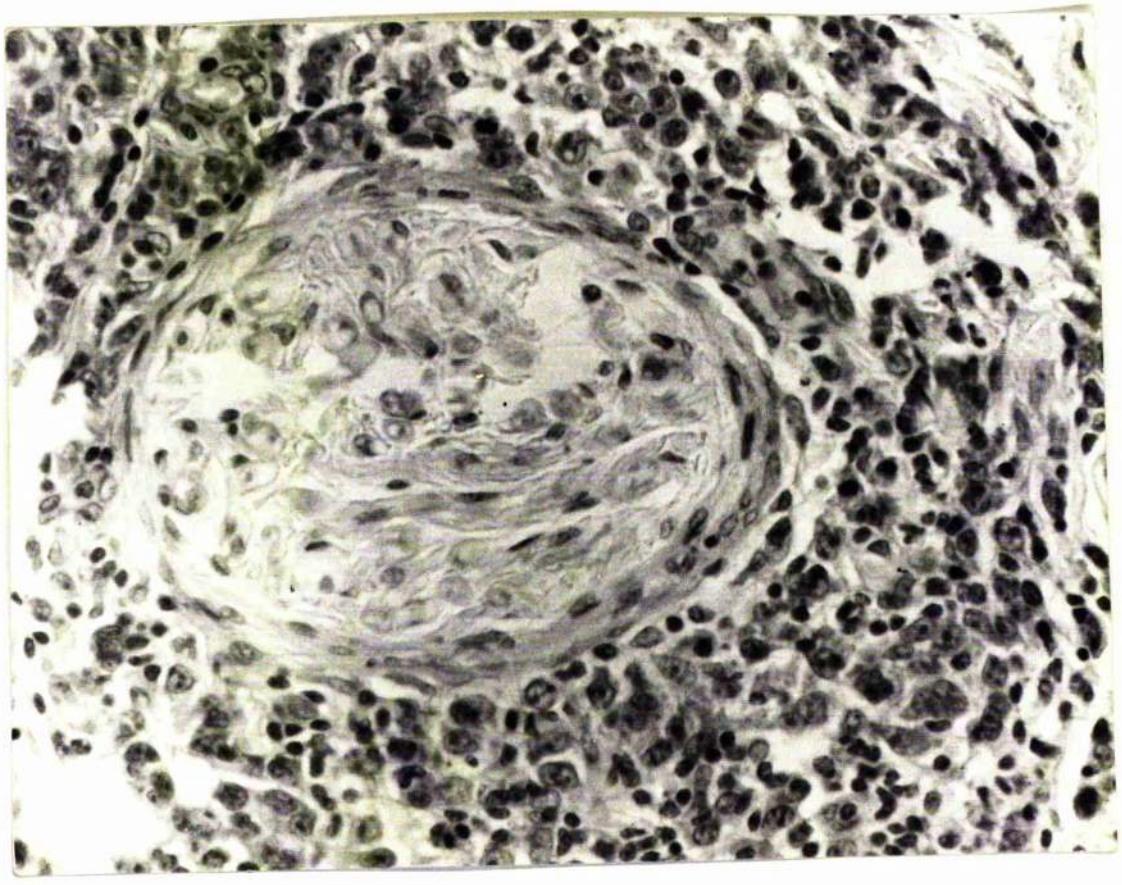


FIGURE 107: Primary Burkitt's lymphoma of breast. Observe perineural invasion by undifferentiated lymphoid cells.

Haematoxylin and eosin X 290.

PLATE 108.

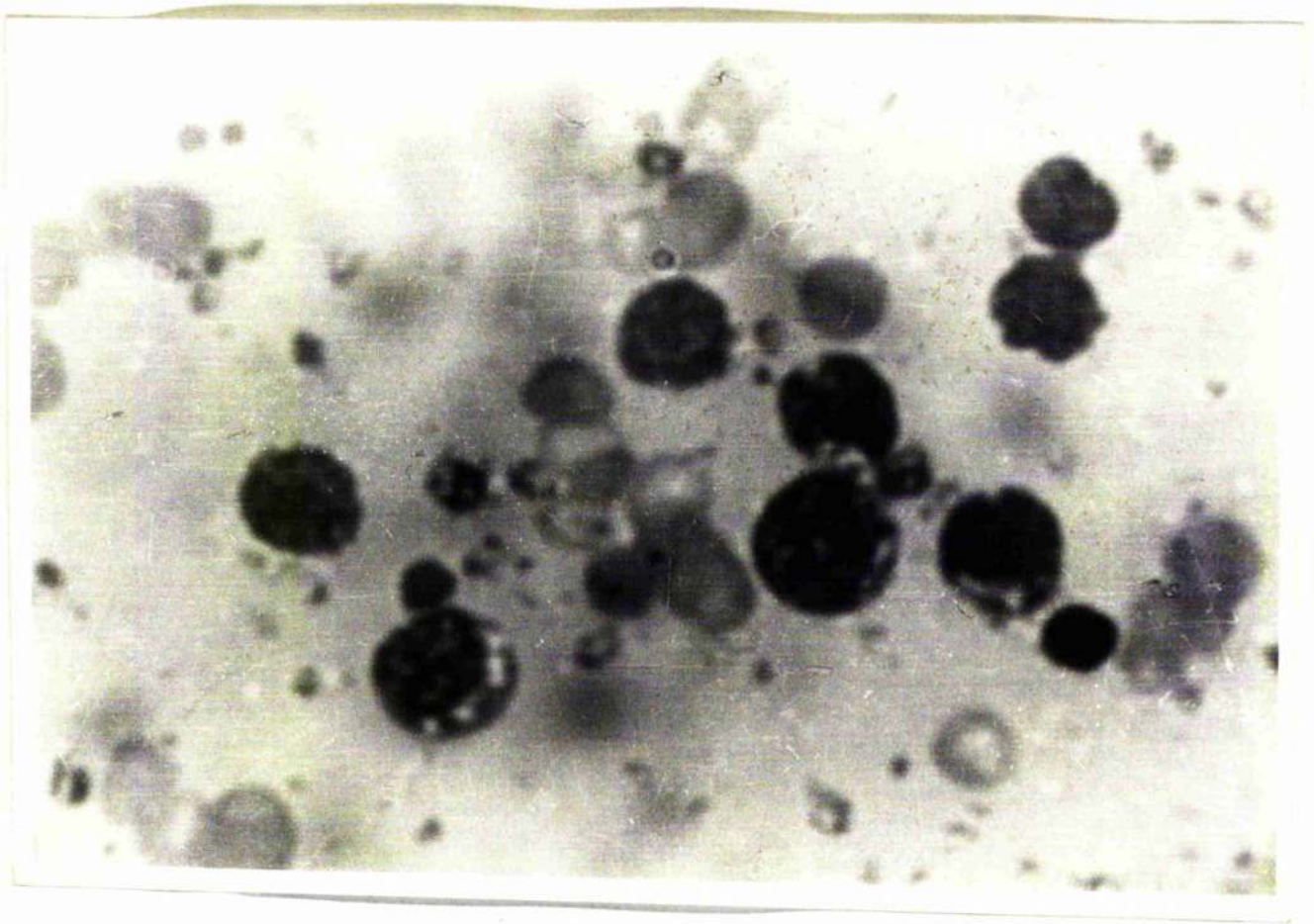


FIGURE 108: Neutral fat vacuoles in undifferentiated lymphoid cells of Burkitt's lymphoma.

May-Grunwald stain X 440.

PLATE 109.

FIGURE 109: Reticulum cell sarcoma. Diffuse proliferation of neoplastic cells with numerous phagocytosing cells.

Haematoxylin and eosin X 100.

PLATE 110.

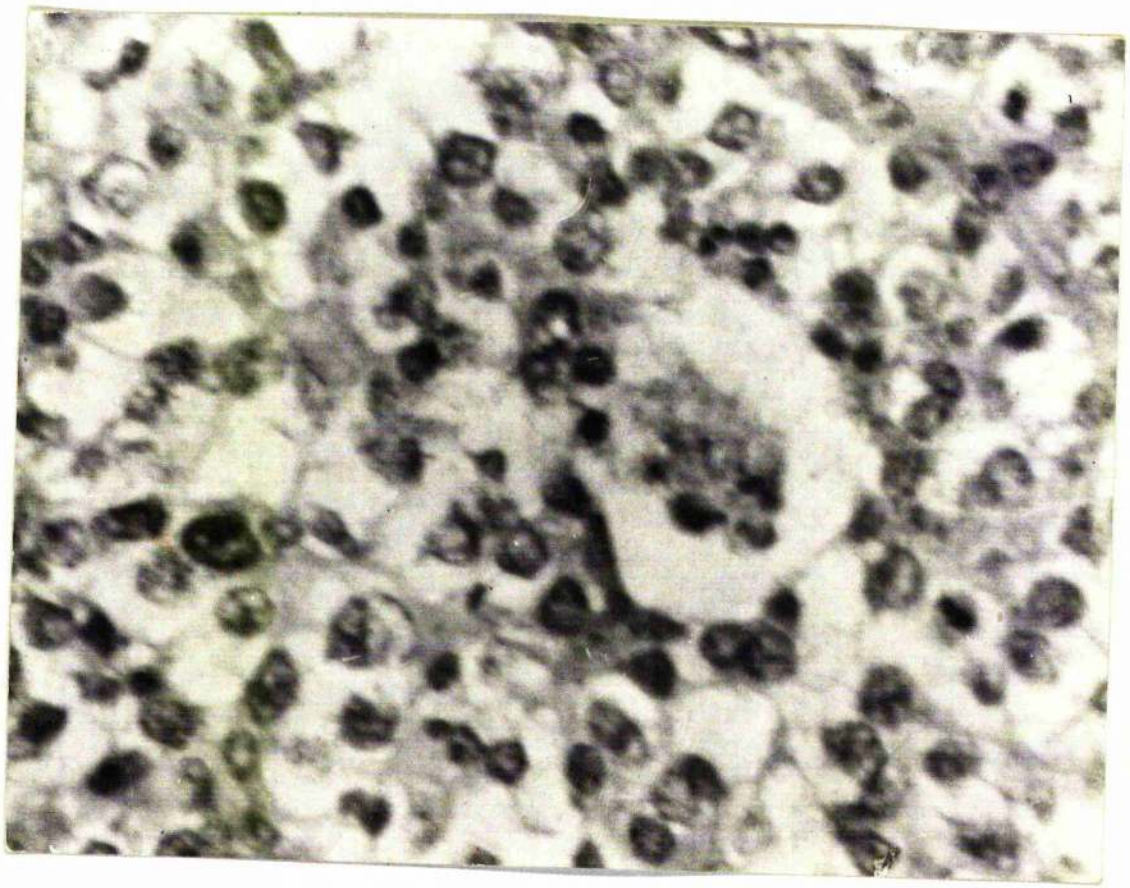


FIGURE 110: Reticulum cell sarcoma. Observe atypical giant cell with vacuolated cytoplasm (right).

Haematoxylin and eosin X 440.

PLATE III.

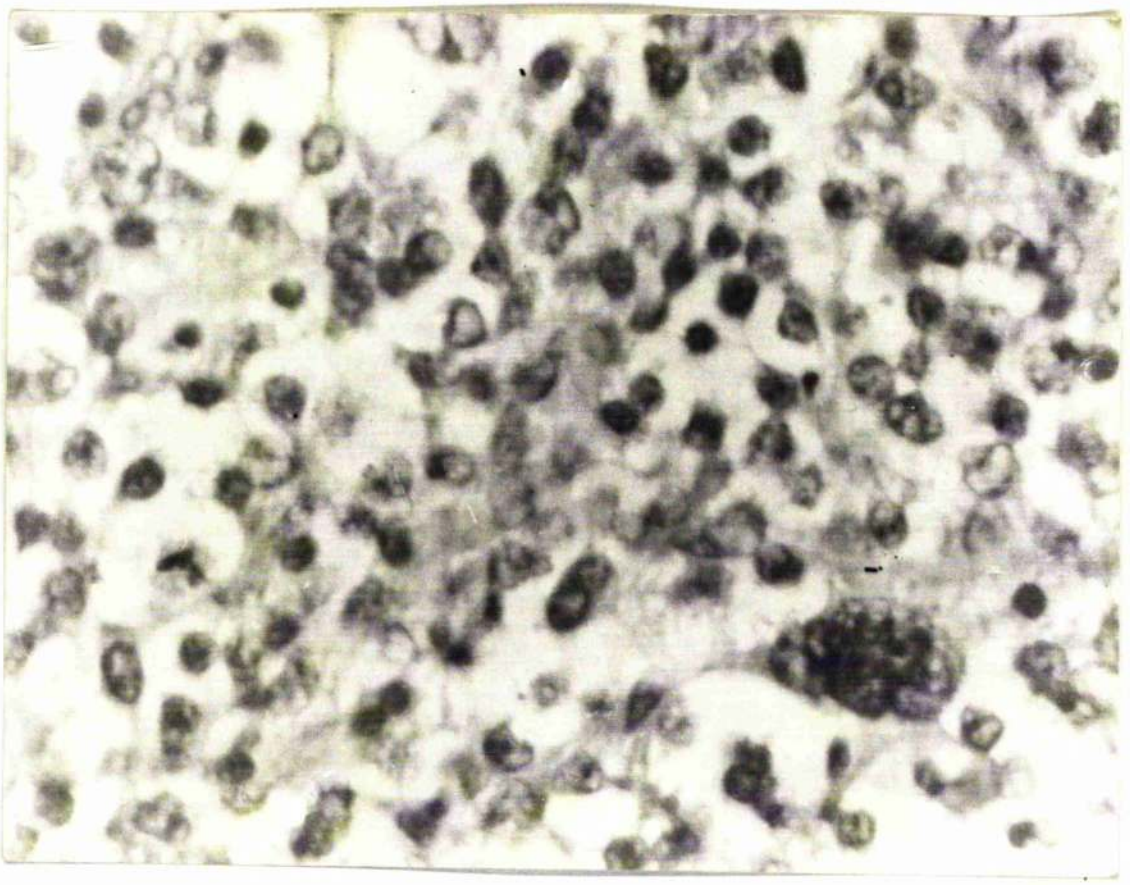


FIGURE 111: Reticulum cell sarcoma. Multinucleated giant cell among profiferating cells with abundant cytoplasm and distinct nuclear membrane.

Haematoxylin and eosin X 440.

PLATE 112.

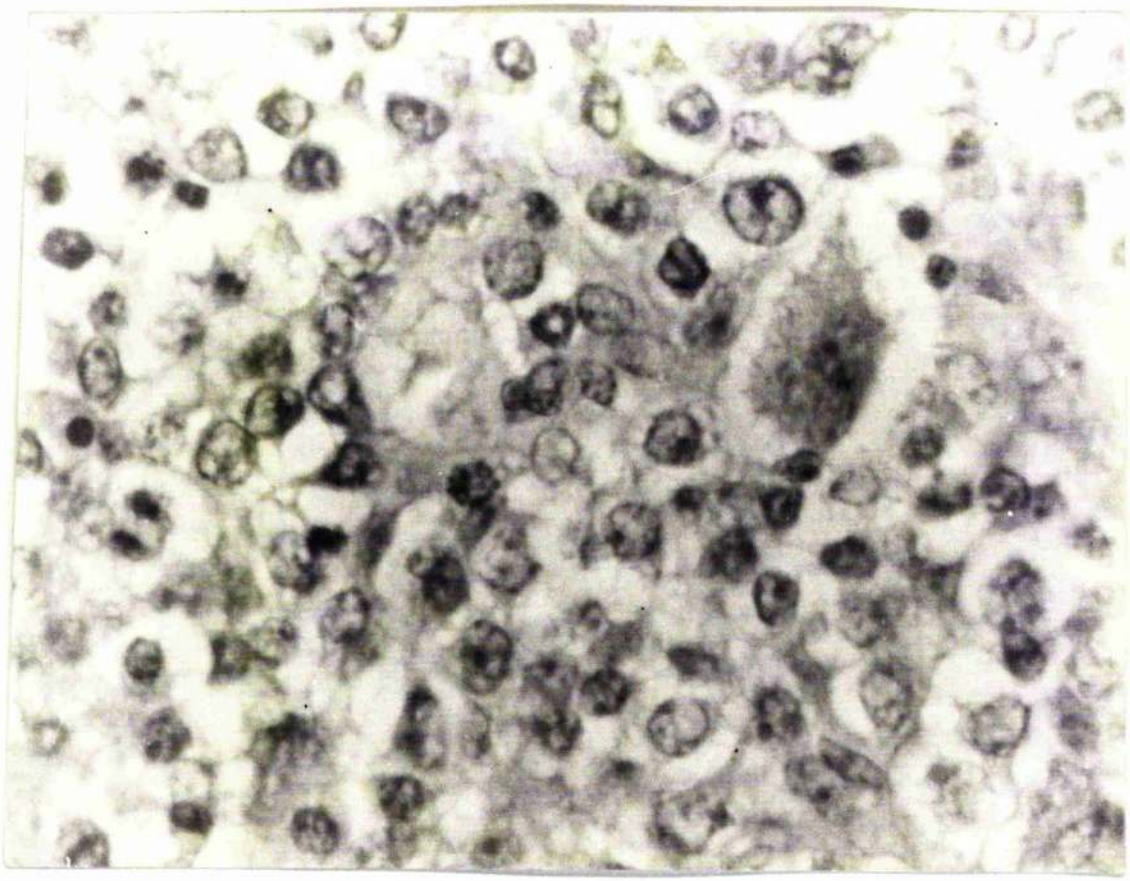


FIGURE 112: Another field of same lesion as fig. 111. Haematoxylin and eosin X 440.

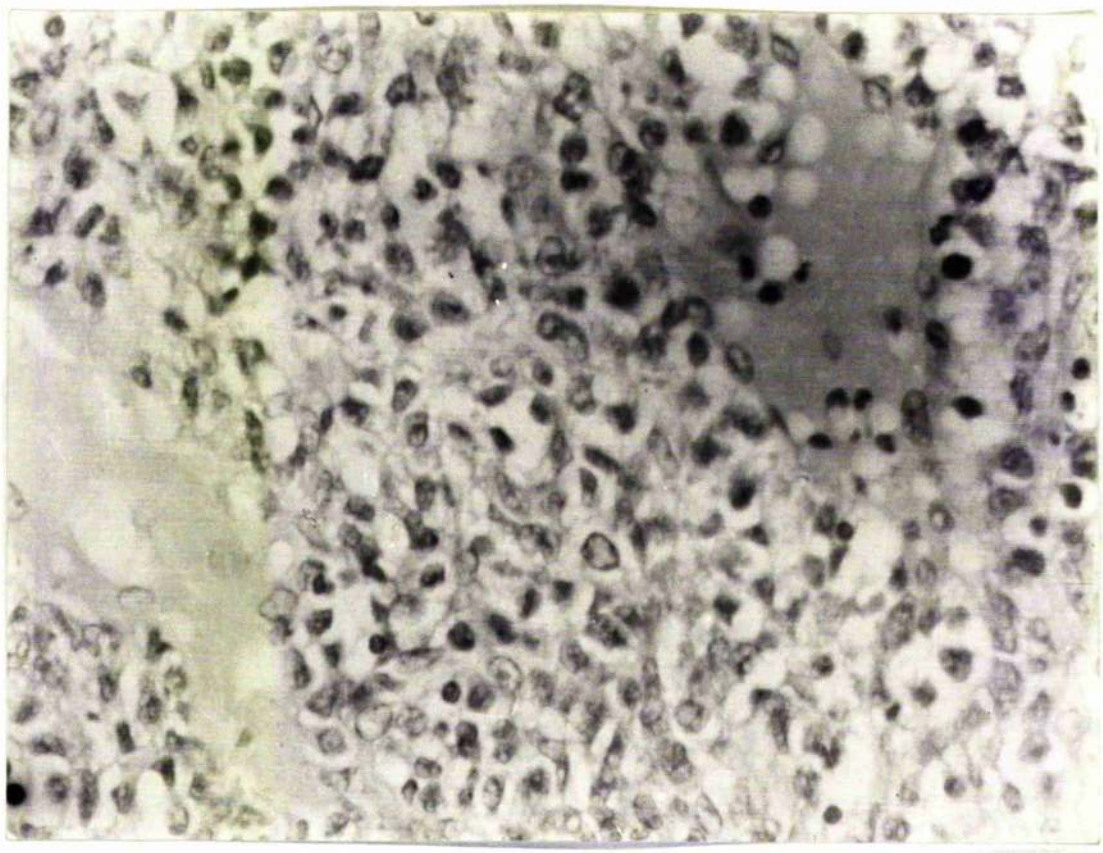


FIGURE 113: Reticulum cell sarcoma. Liquefaction necrosis, (upper, right, and lower, left).

Haematoxylin and eosinX 290.

PLATE 114.

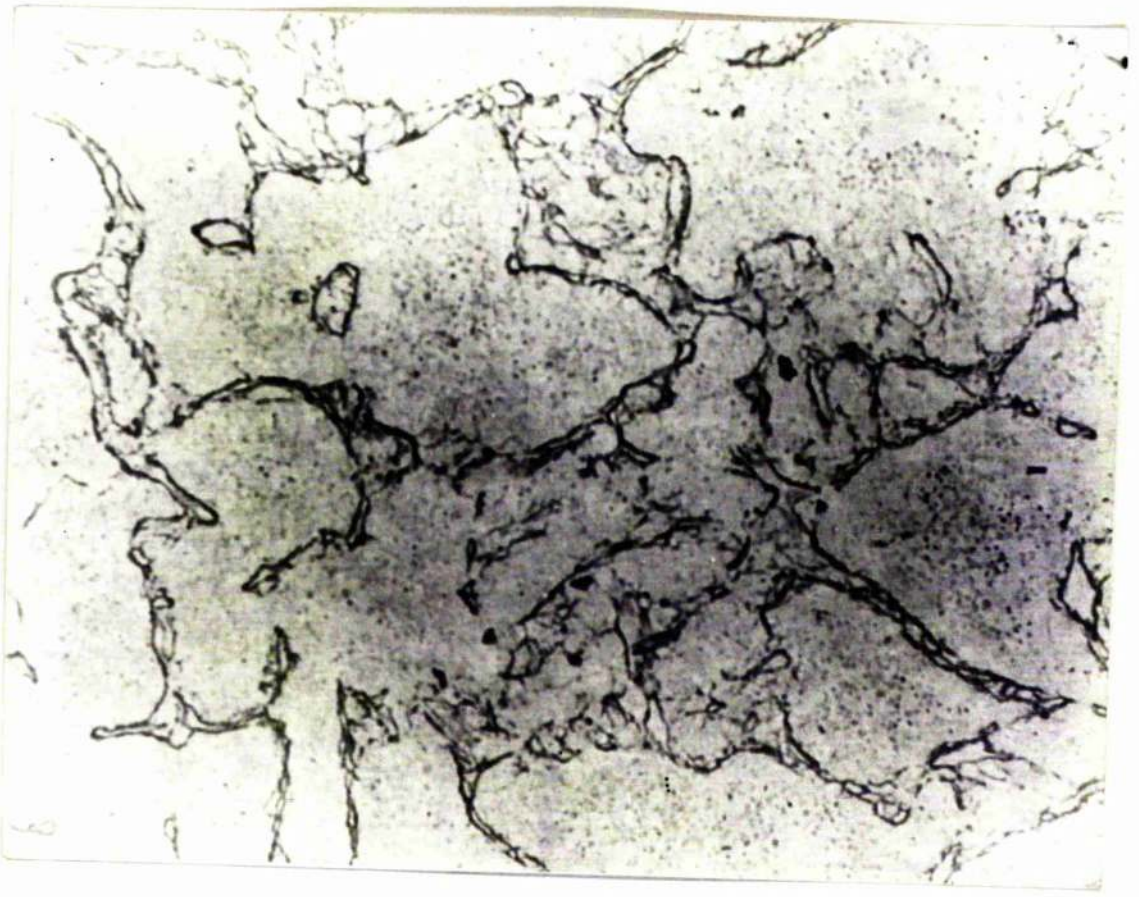


FIGURE 114: Reticulum cell sarcoma. Observe relative scarcity of reticulum fibres which, here, may represent remnants of pre-existing stroma.

Silver impregnation for eticulin X 100.

PLATE 115.

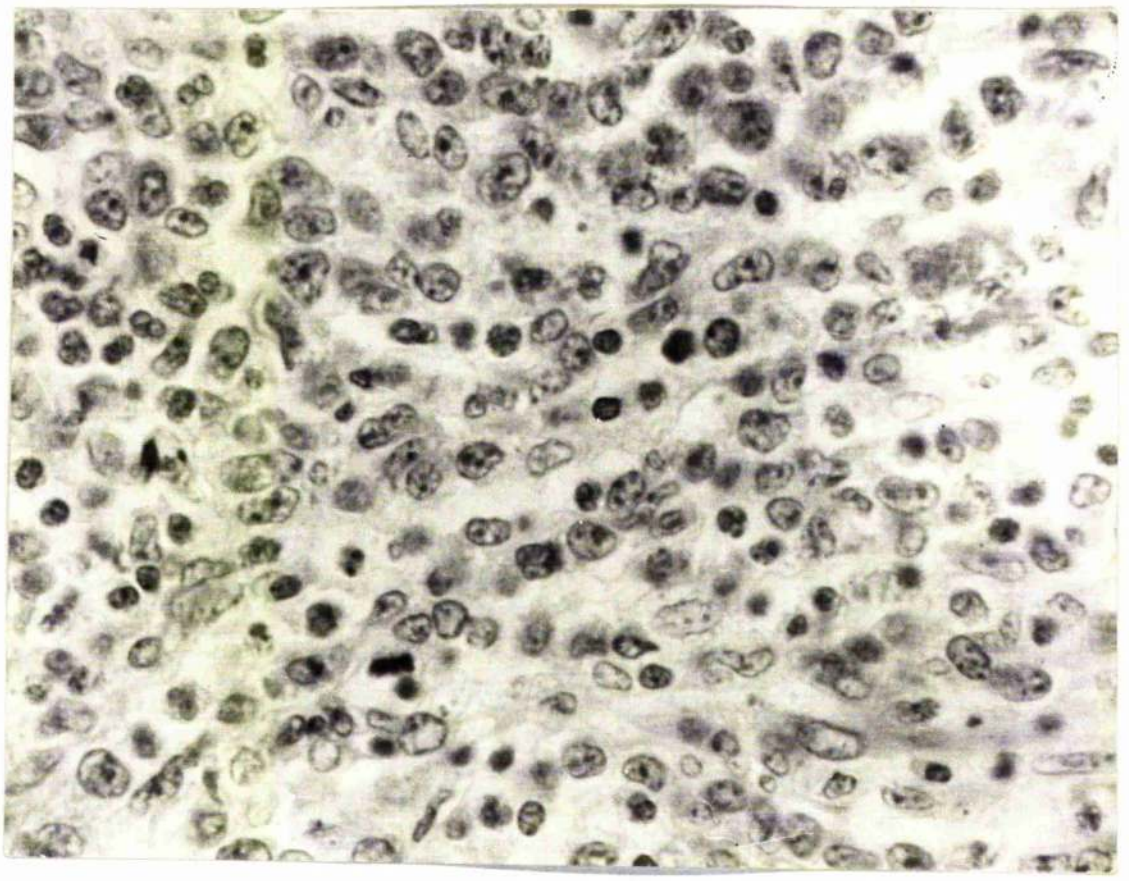


FIGURE 115: Reticulum cell sarcoma metastatic to ovary (Case No. 2).

Haematoxylin and eosin X 290.

PLATE 116.

FIGURE 116: Reticulum cell sarcoma metastatic to ovary (Case No. 2). The malignant cells have clear abundant cytoplasm.

Haematoxylin and eosin X 440.

PLATE 117.

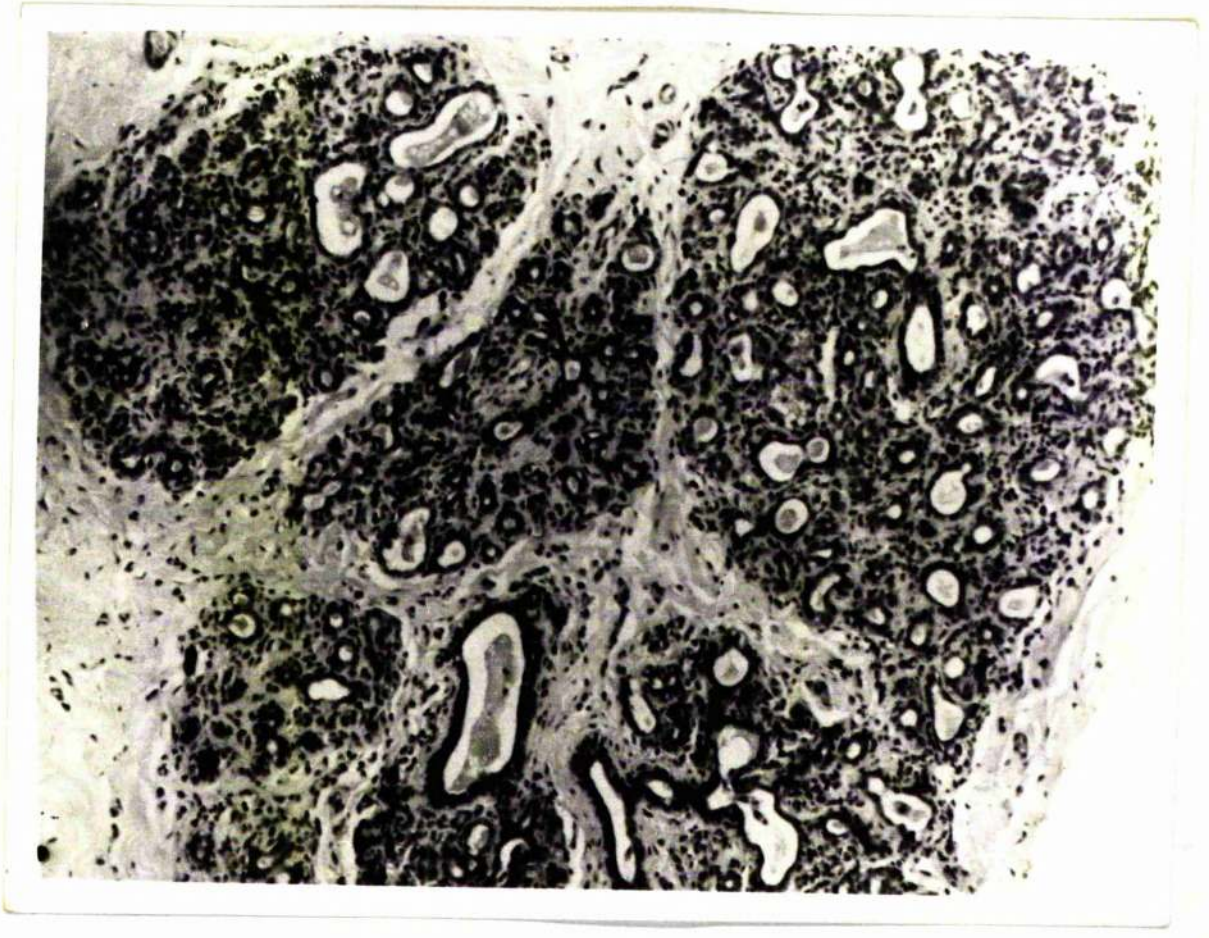


FIGURE 117: An area of adenosis in fibrocystic disease of breast. Observe moderate lympho/plasma cell infiltration.

Haematoxylin and eosin X 200.

PLATE 118.

FIGURE 118: Another area of same lesion as fig. 117 showing increased lympho/plasma cell infiltration. Observe disruption of lobular pattern by proliferating ducts and ductules.

Haematoxylin and eosin X 100.

PLATE 119.

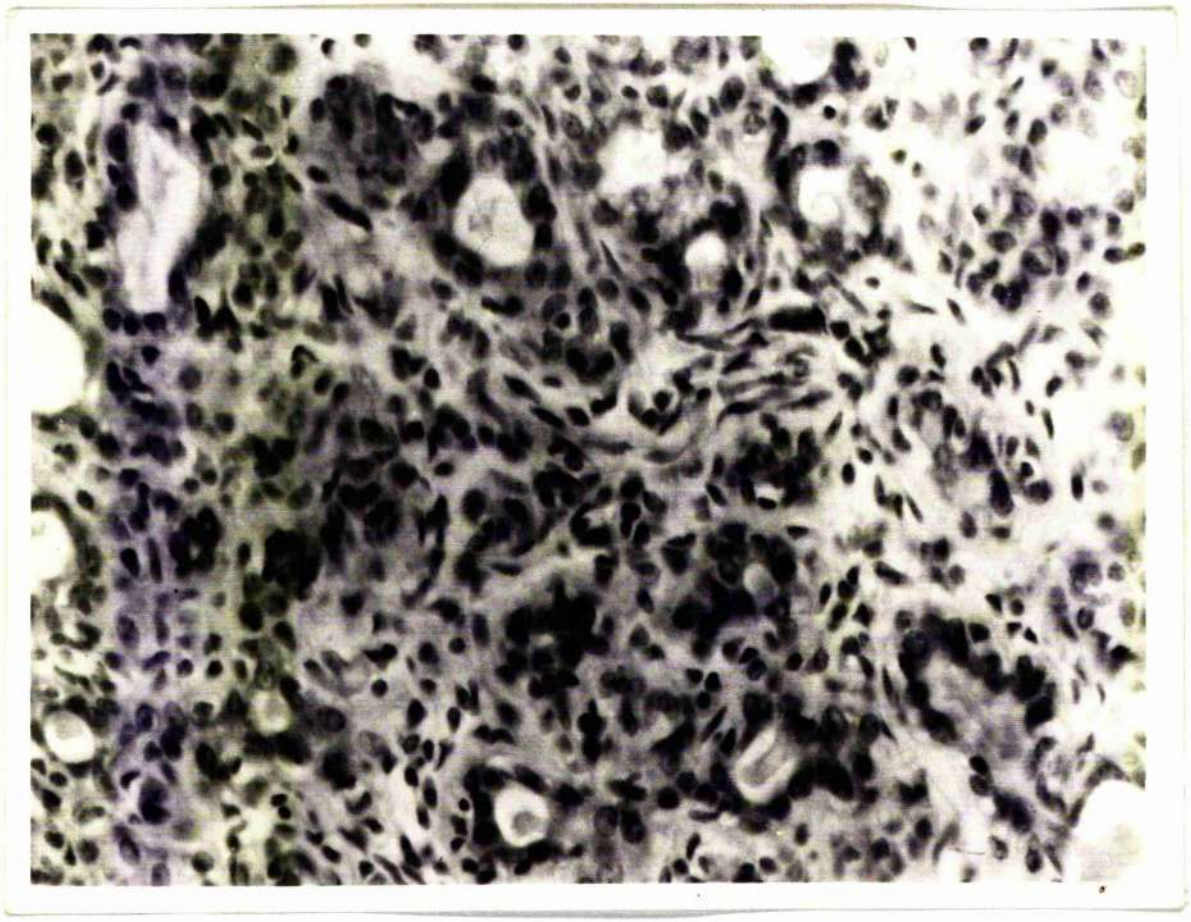


FIGURE 119: High-power view of fig. 118 showing dysplastic proliferating ductules and ducts.

Haematoxylin and eosin X 290.

PLATE 120.

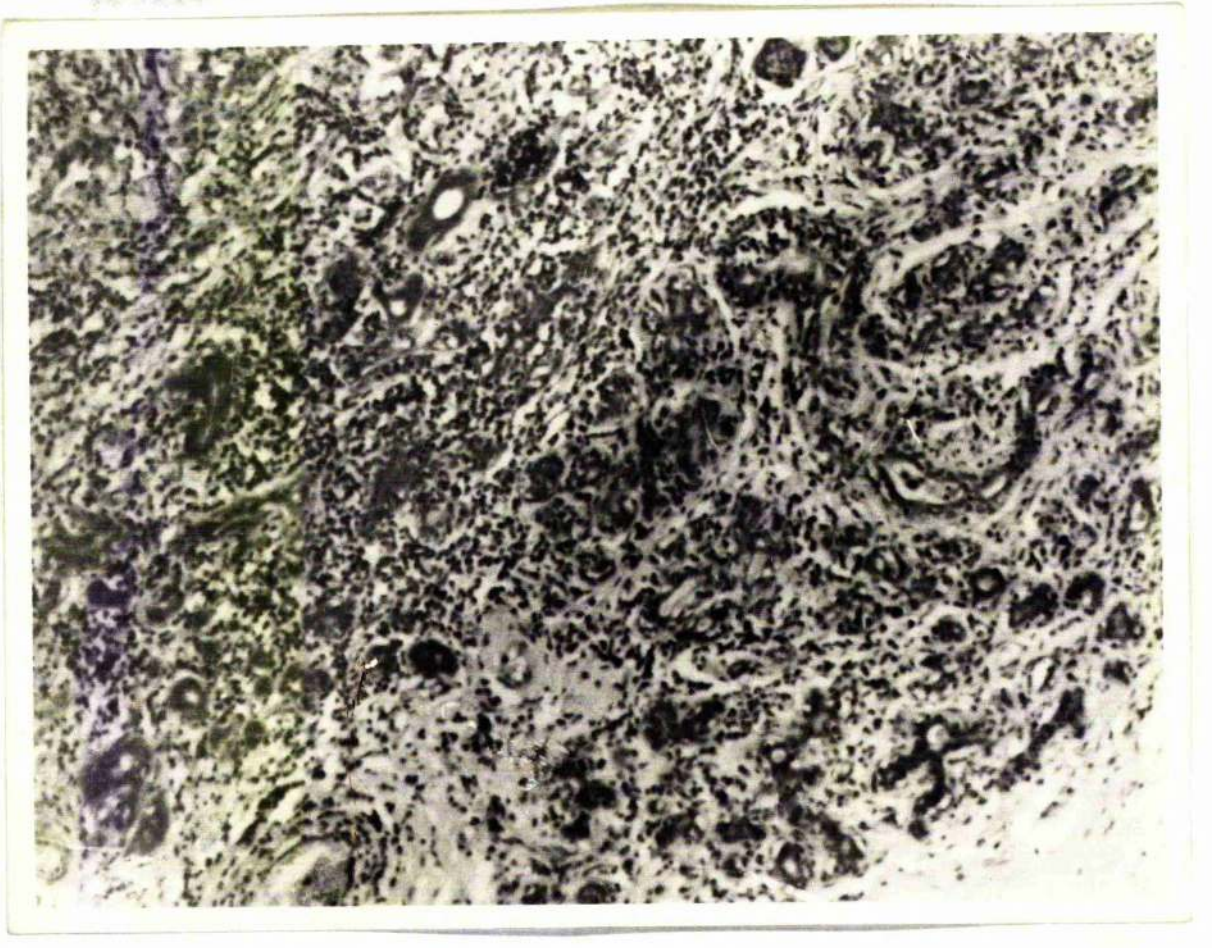


FIGURE 120: Malignant ducts and ductules heavily infiltrated by lympho/plasma cells (middle left.

Haematoxylin and eosin X 100.

PLATE 121.

FIGURE 121: Adjacent proliferating areas becoming confluent to form satellite medullary carcinoma.

Haematoxylin and eosin X 100.

PLATE 122.

Evolution of meddullary & circumscribed Carcinoma

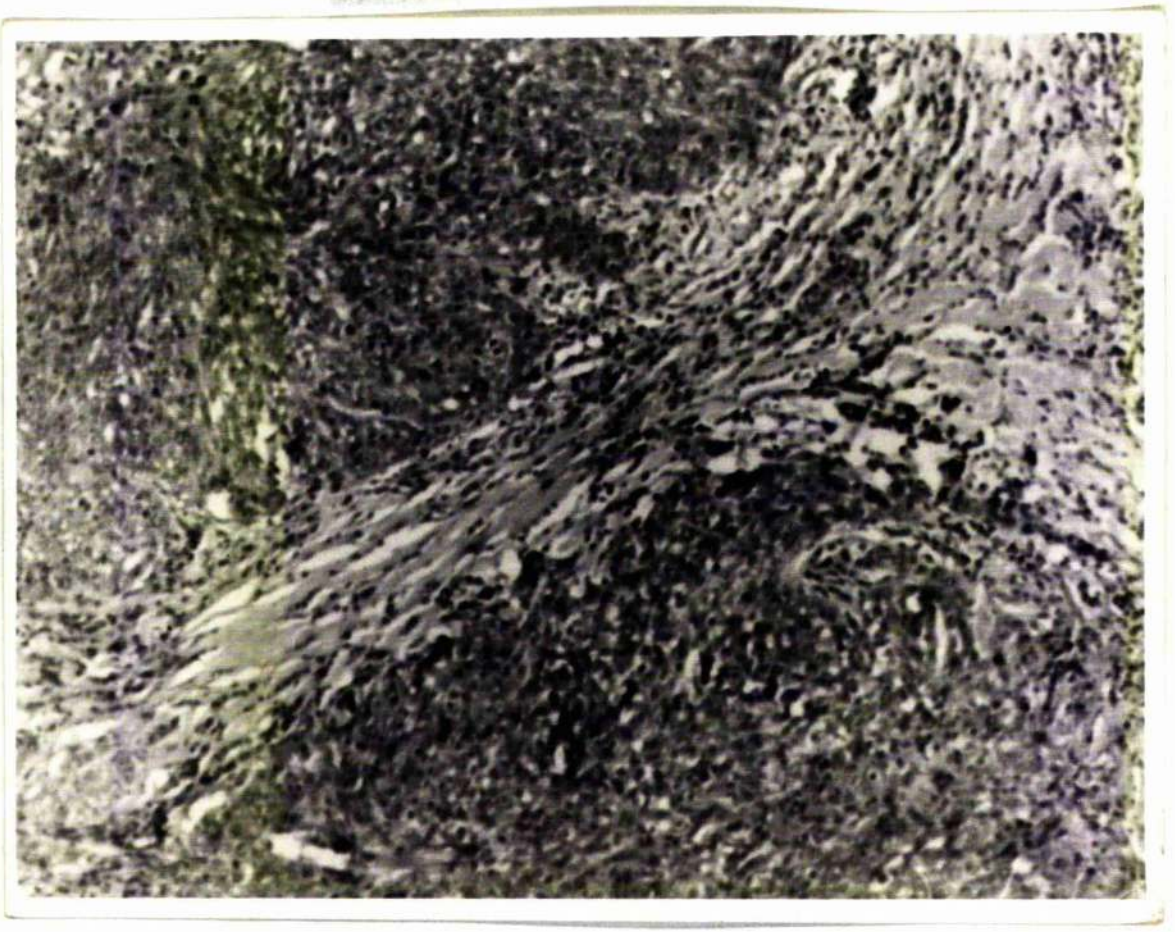
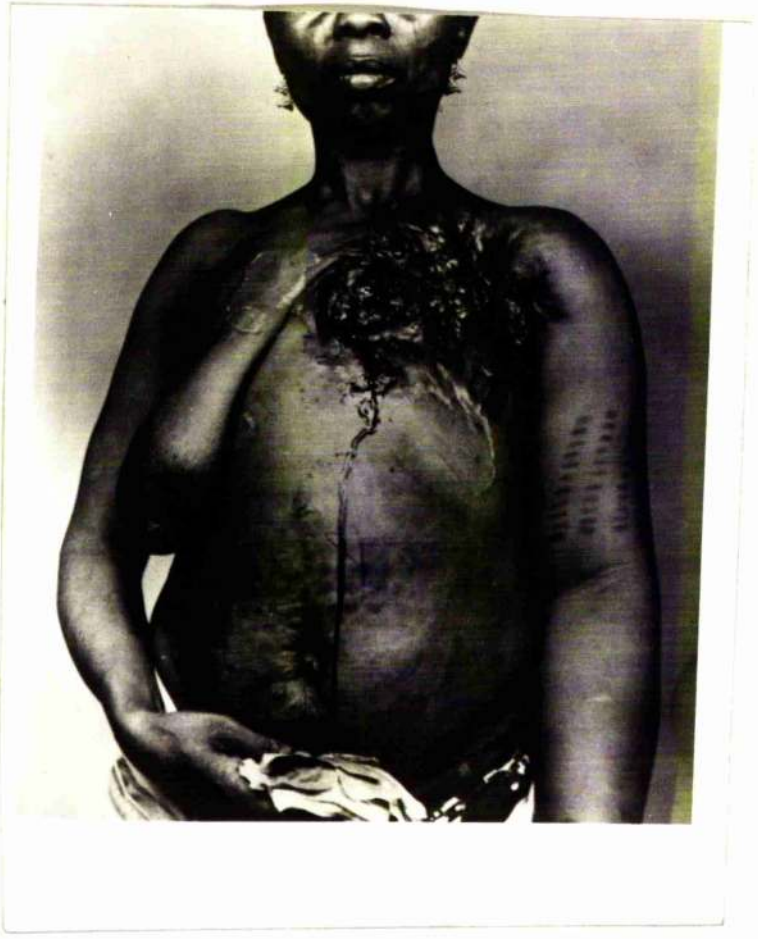


FIGURE 122: Progression of lesion to form either Medullary carcinoma with adjacent malignant lobules coalescing (left corner) or, lobulated circumscribed carcinoma.

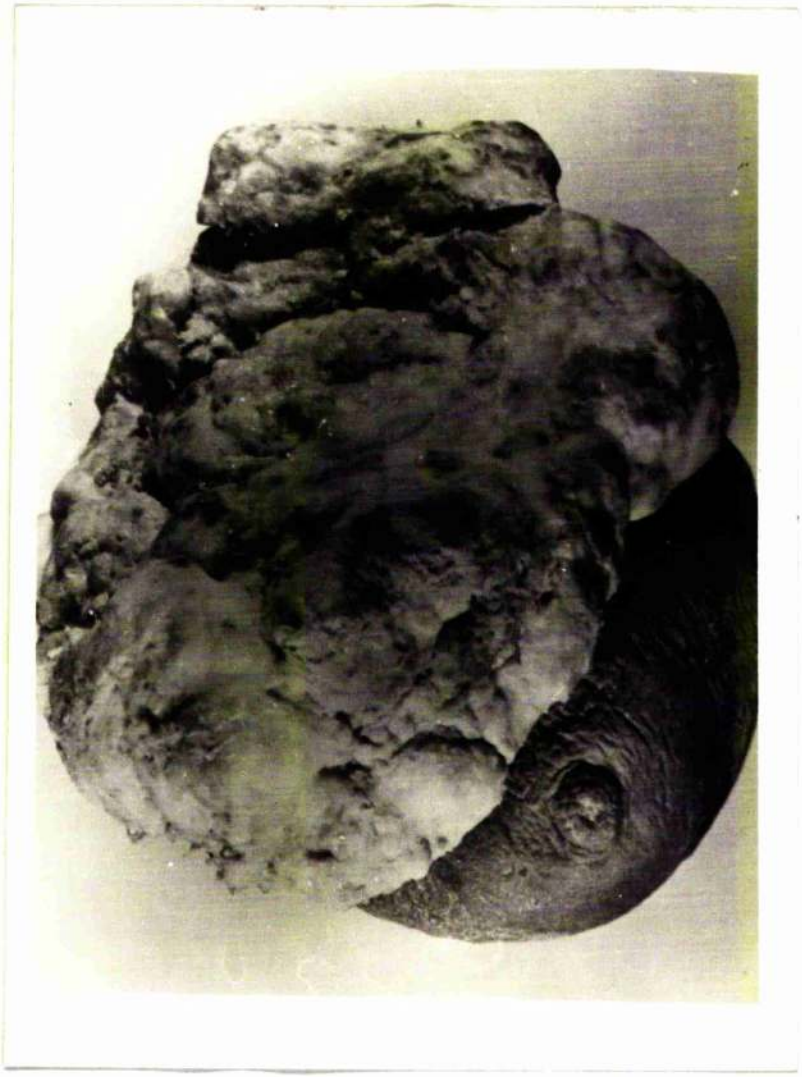
Haematoxylin and eosin X 100.

APPENDICES 19-24: CLINICAL AND GROSS PATHOLOGICAL FEATURES OF BREAST CANCER.

PLATE 123.

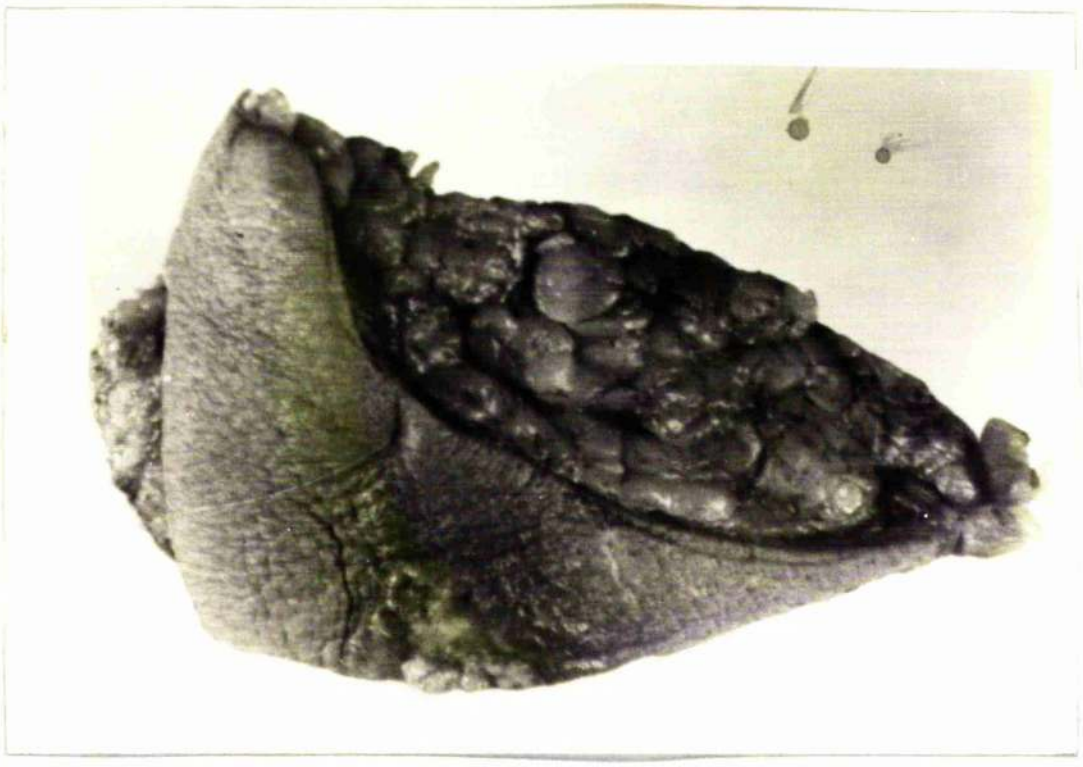


PHOTOGRAPH 1: Auto-amputed left breast due to carcinoma. Observe lymphoedema of upper limb; By courtesy of Professor J. Ajayi (Survgry Dept., U.C.H., Ibadan).



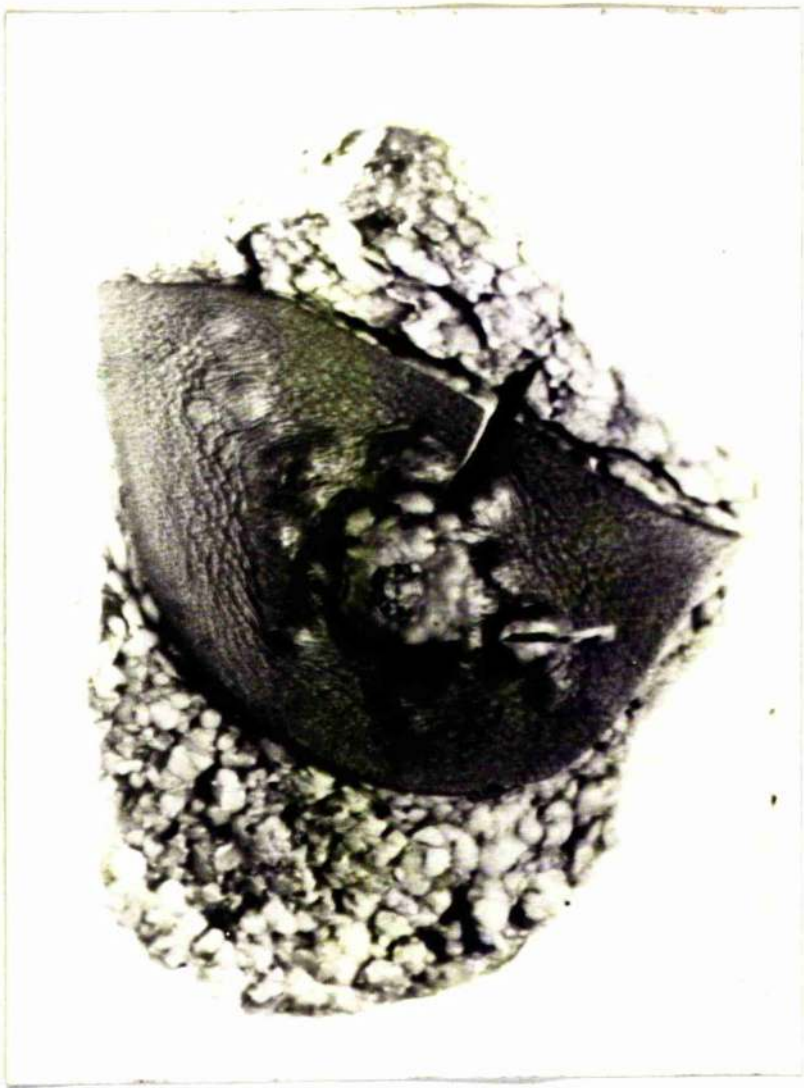
PHOTOGRAPH 2: Fungating breast carcinoma secondarily infected.

PLATE 125.



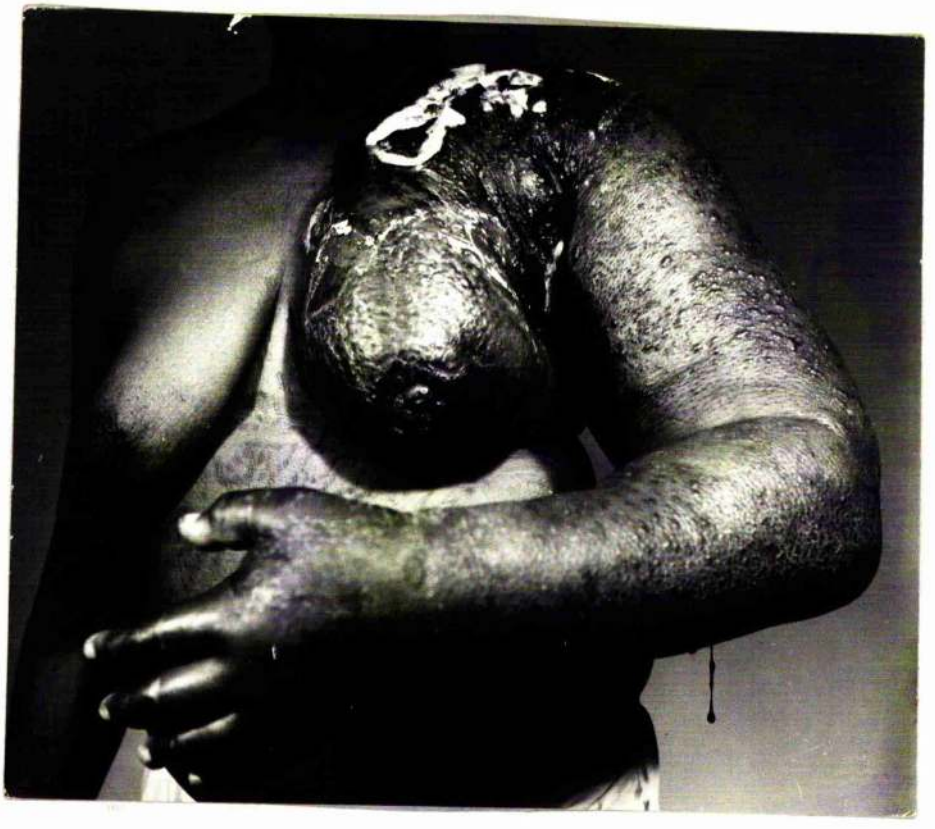
PHOTOGRAPH 3: Nipple and surrounding alveolar destruction in male breast carcinoma.

PLATE 126.

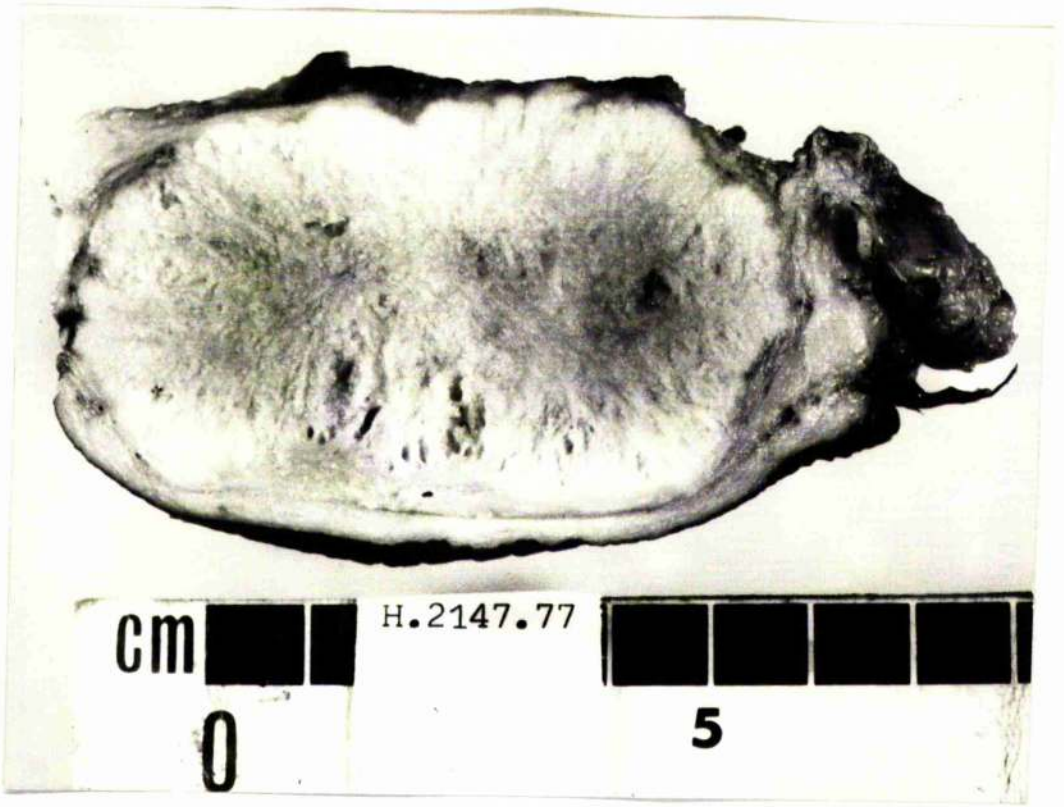


PHOTOGRAPH 4: **Multiple malignant nodules in and around the nipple and areolar of a male breast. By courtesy of Professor A. A. Abioye (Department of Pathology, U.C.H., Ibadan).**

PLATE 127.

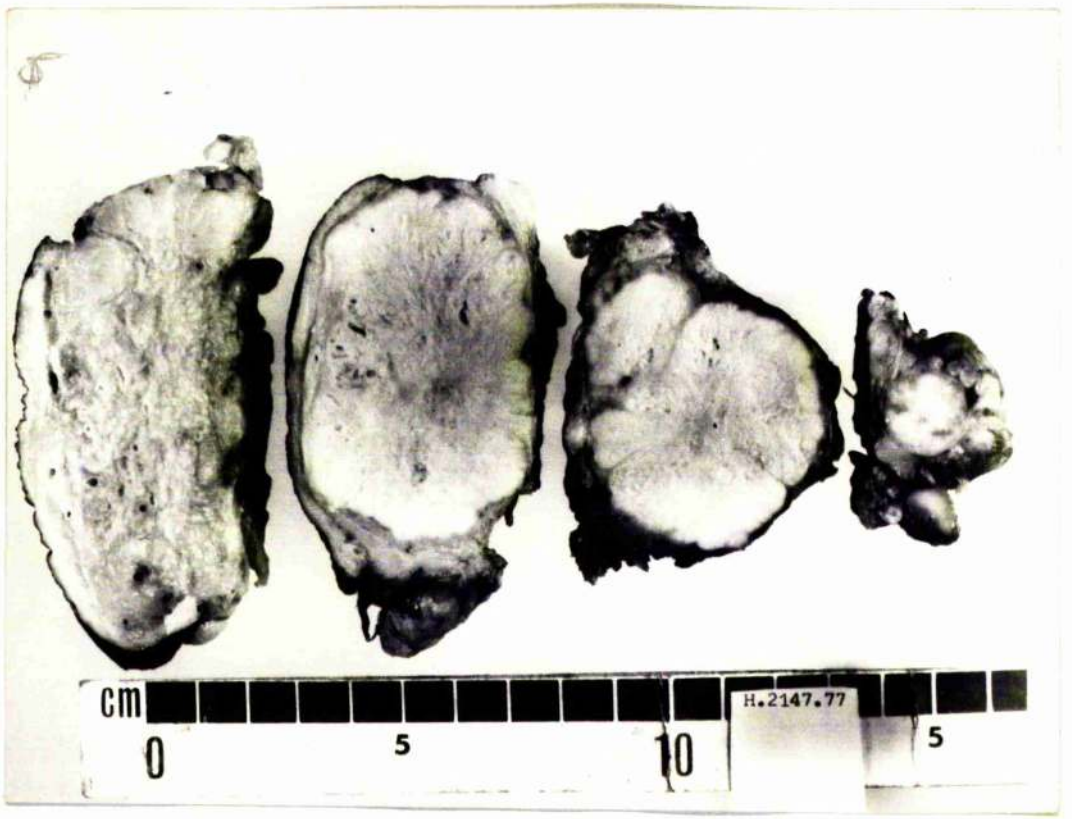


PHOTOGRAPH 5: Carcinoma of the breast, massive lymphoedema of the left upper limb.
By courtesy of Mr. E.O. Kalejaiye,
(Surgery Department, U.C.H., Ibadan).



PHOTOGRAPH 6: Well circumscribed breast carcinoma replacing the mammary parenchyma.

PLATE 129.



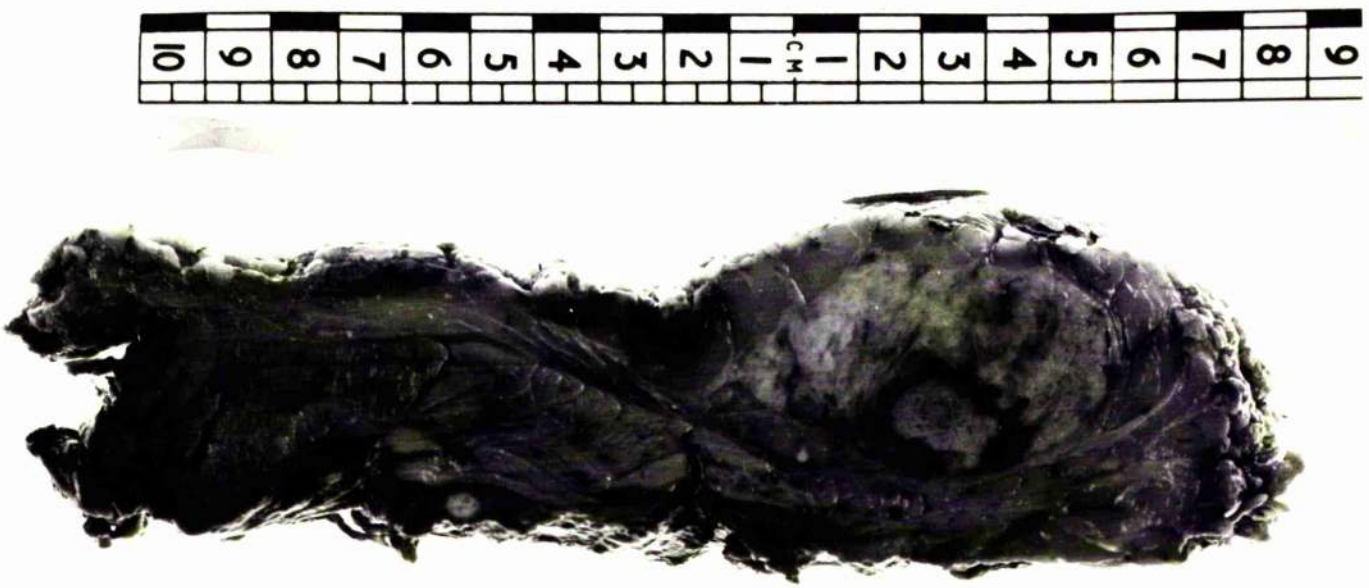
PHOTOGRAPH 7: Serial section of well circumscribed breast carcinoma involving the axillary lymphnodes.

PLATE 130.

PHOTOGRAPH 8: Cystic degeneration in a well circumscribed carcinoma of the breast. By courtesy of Late Dr. J.O. Smith (Department of Pathology, U.C.H., Ibadan).

PLATE 131.

PHOTOGRAPH 9: **Multilobulated breast carcinoma with unceration and areas of haemorrhage. By courtesy of Late Dr. J.O. Smith (Department of Pathology, U.C.H., Ibadan).**



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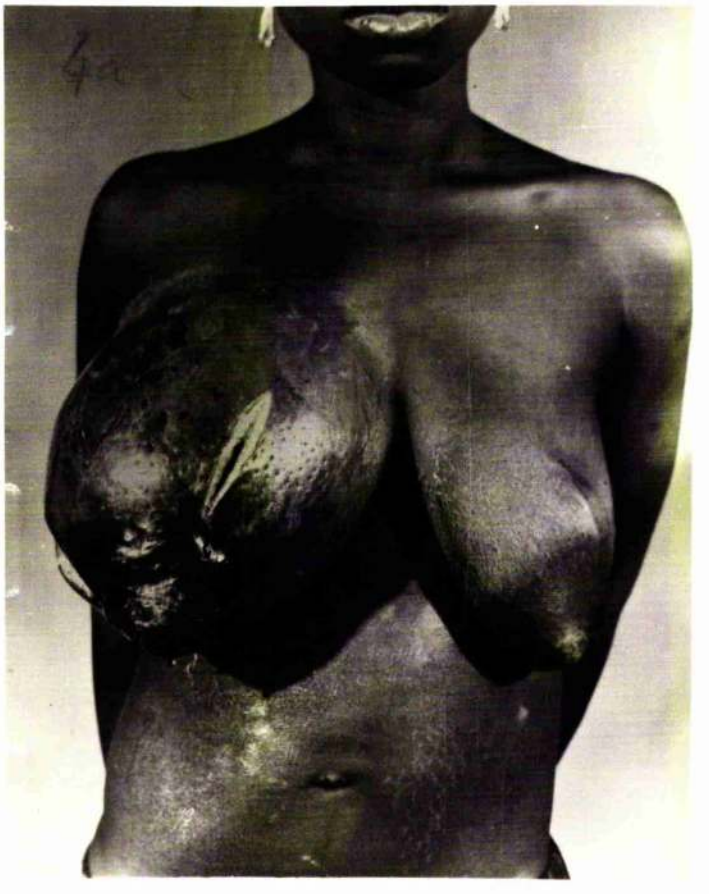
PHOTOGRAPH 10: **Muscular invasion of breast carcinoma in a male breast lesion.**

PLATE 133.

PHOTOGRAPH 11:

Primary Burkitt's lymphoma of breast. Observe multiple ulcerated malignant nodules in left upper quadrant of the breast. By courtesy of Mr. J.I. Durodola (Dept. of Surgery, U.C.H., Ibadan).

PLATE 134.



PHOTOGRAPH 12:

Reticulum cell sarcoma observe diffuse enlargment of right breast peau de orange in the skin. By courtesy of Mr. J. I. Durodola (department of Surgery, U.C.H., Ibadan).

PLATE 135.

PHOTOGRAPH 13:

Lateral view of photograph 12. Observe multiple incisions in the two photographs made in an attempt to drain a breast "abscess".